Section of Proctology

President R W Nevin TD FRCS

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Discussion on Megacolon and Megarectum with the Emphasis on Conditions other than Hirschsprung's Disease

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Megarectum and megacolon have not been discussed since Gardiner's paper on megacolon in 1953. He adopted a classification which seemed generally acceptable, namely: (1) Obstructive or symptomatic (including C.N.S. lesions). (2) Aganglionic or Hirschsprung's disease. (3) Simple (also known as functional) – idiopathic, pseudomegacolon, dolichocolon, colon inertia. A better name for the second type should be a more-embracing term, rather than 'aganglionic' or 'achalasic', to include all abnormalities of the ganglion population: for in Hirschsprung's disease no ganglia are found in a segment and in Chagas's disease, due to the *Trypanosoma cruzi*, there may well be a quantitative diminution of ganglia. Gardiner discussed mainly the simple or functional group; much of this paper is devoted to this group, though the findings are not altogether in keeping with his. It is the presence of the megarectum as well as the megacolon which makes treatment in the adult difficult.

What is megarectum and megacolon? The condition may be defined as a state in which the bowel is persistently much larger in diameter than normal and intractably constipated. Spurious diarrhœa may sometimes be a symptom of this.

Obstructive megacolon and megarectum may occur at any age, from lesions pressing on the bowel wall from outside, such as pelvic tumours, and from lesions in the bowel wall or within its lumen, such as stenosis, strictures and tumours. These can be dealt with by removal of the obstruction; they are not true megacolon. Gardiner included central nervous system lesions such as spina bifida in the obstructive group. Many extensive neurological lesions cause megacolon; these are separate and difficult problems. A fourth type of megacolon should be included as 'disorders of the central nervous system'.

Neurological lesions and the obstructive type have been excluded from this survey which is of 53 cases, 28 cases being documented. Over half of the cases presented before the age of 30, and over a third between the ages of 11 and 30. Excluding those occurring in the first year, 24 were males and 23 were females. In the first year of life all were males: 5 presented during the first weeks of life, all due to Hirschsprung's disease; 1 started at five weeks and was thought to be functional.

There were 8 cases of Hirschsprung's disease in the adult proven by adequate rectal biopsy and 1 possible case where no biopsy was done. All the definite Hirschsprung's disease cases were male; the possible case is the only female. All were aged between 21 to 40 except 1, whose operation was carried out at the age of 13. Hirschsprung's disease in the adult is not uncommon. The aganglionic segment appears to be confined to the rectum and has not, as yet, extended far into the sigmoid. I have not seen any case of a colonic aganglionic segment without rectal involvement and most of such cases recorded are inadequately documented. The Swenson-type pull-through procedure in the adult is formidable, as the pelvis is much deeper than that of a child and the colon has reached gigantic proportions, perhaps up to 25 cm in diameter, and the bowel wall may be 4–6 mm thick. If a pull-through such as a Maunsell-Weir abdomino-anal procedure can be accomplished, the colon is apt to remain adynamic, as sometimes occurs in the infant and perhaps related in ætiology to that seen in neonatal intestinal obstruction (Nixon 1960).

The results of surgery for Hirschsprung's disease in the adult, at St Mark's and St Bartholomew's Hospitals, are not very good. Three of the 4 cases treated by anterior resection have poor results as they require frequent enemata; the fourth has a fair result but the bowel above the anastomosis remains loaded. These cases may

recur, as only a small part of the aganglionic segment was removed. One patient was treated by a Marden Black pull-through operation but though his bowels move he is not truly or adequately continent. Three cases have good results: 2 had abdomino-anal operations and the bowels move normally but one is impotent; the third is the questionable case of Hirschsprung's disease treated by colectomy and ileorectal anastomosis (a boy operated on at 13 years, who had a good result from a modified Swenson-type pull-through procedure, is excluded).

I wish to stress the fact that though most cases of Hirschsprung's disease present in the neonatal period, not all do so; if possible cases occur later an adequate rectal biopsy should be taken and if no ganglia are found an operation advised. It is doubtful if medical management should be advised permanently once a diagnosis of Hirschsprung's disease has been established, for sooner or later operation will become mandatory.

The simple or functional group of megacolon and megarectum when they reach adult life are difficult. In the child corrective training may achieve temporary improvement in a majority. Lee *et al.* (1950), Ravitch (1958*a*,*b*) and Hallenbeck & Waugh (1952) all agree that medical management is correct, except in cases with a long sigmoid, the dolichocolon which intermittently twists. This is in keeping with Gardiner's observations and sigmoid resection is advised for these cases. This medical management or sigmoid resection is not the answer for all and attention to clinical findings and the macroscopic appearance at laparotomy is rewarding. There is an inconsistency in the literature in regard to the condition of the anus in the functional case. Many times the anus is said to be relaxed and even gaping with soiling of the clothes, yet at other times a remark appears such as 'if the anus is spastic it must be dilated and if need be a sphincterotomy carried out'. Surely these two conditions are not one and the same disease.

Three different and distinct macroscopic appearances of the distal colon and rectum may be found: (1) Dilated and relatively thin-walled sigmoid, frequently associated with a rectum which appears normal or a little dilated. There is almost no true muscular hypertrophy of the bowel wall. (2) A dilated and grossly hypertrophic sigmoid and a dilated *atonic* or *hypertonic* rectum. It may be argued that one cannot appreciate bowel tonus, but this is, to some extent, possible clinically. Some cases do not seem to fit into these categories. The dilated thin-walled sigmoid is typical of dolichocolon, as Hallenbeck & Waugh (1952) pointed out. The volvulus which occurs in these people, and may be confirmed by scarring of the elongated mesentery, is intermittent; hypertrophy does not occur to any degree. The rectum is often a little dilated and sigmoidoscopy is easy, but this may be a reflex atonicity resulting from the mesenteric twist. These cases respond to sigmoid resection. Their history is often suggestive, with periods of intermittent obstruction. The anus is normal in appearance and to digital examination. Rectal sensation and the response to rectal distension are normal also.

In the dilated hypertrophic sigmoid and rectum there is frequently a history of bowel actions perhaps once a month. This type is not common but suggests distal obstruction and the anus is usually competent and unrelaxing. Strangely, rectal discomfort is not marked and sensation may be diminished in spite of a high rectal tone but the sphincters are not easily inhibited. In these cases with sigmoid and rectal hypertrophy there is failure of sphincteric inhibition, the cause of which is unknown. It is difficult to see what treatment can help until the condition is better understood. There is, however, a failure of physiological function, that is of sphincteric inhibition with rectal distension by fæces; the X-ray appearance often shows a high degree of tone with good segmentation despite the dilatation.

The dilated hypertrophic sigmoid with the dilated atonic rectum is perhaps more common than the previous group. Again the anus is closed. These people have little or no rectal sensation and a failure of sphincteric inhibition, despite a huge degree of rectal distension. Such is a patient who walked about with four litres of fluid in the rectum and large bowel without sensation or leakage. The balloon with which an attempt was made to register rectal sensation burst in her rectum without any response and she was not mentally abnormal. The rectal wall sensory mechanism apparently failed though no bladder upset was apparent. The treatment of these cases is a problem too.

Before resecting a megacolon it is advisable to make sure that (1) ganglia are present in a rectal biopsy, (2) rectal sensation is adequate, (3) rectal volume is not excessive in order to produce a sensory and reflex response, and (4) that sphincteric inhibition occurs with rectal distension. These investigations are essential if sphincteric tone is normal. The only cases, if obstruction is excluded, where the condition may be due to bad habit, psychological or mental disturbance are those in which soiling of the clothes is present. These cases show some diminution of rectal sensation requiring an increased volume of fæces to initiate it, but the sphincters are inhibited normally.

Senile rectal atony, with its consequent fæcal impactions in which propulsion fails, exhibits inhibition of the sphincters. Thus it, too, should be automatically excluded from those cases where surgery is to be considered. A trial of Prostigmin

is often helpful and may give a promising response in functional megacolon. The results, however, have not been lasting.

Abnormalities of rectal physiology which are associated with megacolon and megarectum have been mentioned – the hypertrophic megarectum, the atonic megarectum and failures of sphincteric inhibition. Clearly these are abnormalities of rectal function and colonic resections do little to improve them; it may make them worse, as a relatively more hypertonic colon is anastomosed to a relatively inert rectum. Colonic resections for these abnormalities are likely to meet with the same result as they did in Hirschsprung's disease when surgeons failed to appreciate the presence of a rectal obstructing lesion. In a series of 14 cases of ileorectal, ileosigmoid and cæcorectal anastomoses, sigmoid and anterior resections, 9 still have a loaded rectum requiring enemata to clear them and 2 have diarrhœa. Six ganglionectomies have been carried out, together with other procedures, and no beneficial results have been noted. Abdomino-anal procedures seem to offer better results. Chronic volvulus with a relatively thin-walled colon responded to sigmoid resections.

Two cases bear out Ravitch's observations, one with latent cretinism and one with myxœdema. The bowel habit was improved and the megacolon became less marked with thyroid therapy.

Thus a complete classification of megacolon is reached (Table 1).

Table 1
Classification of megacolon and megarectum

(1) Obstructive: Tumours, strictures, volvulus, &c.
(2) Faulty habits, including psychiatric problems
(3) Endocrine: Cretinism, myxœdema
(4) Central nervous system: Spina bifida, paraplegia, cauda equina, &c.
(5) Peripheral nervous system: Absent ganglia, reduced ganglia, abnormal end-organs or reflex response (insensitive rectum, failure of sphincteric inhibition)

Finally, megacolon, when the bowel is opened perhaps only once a month, suggests a disorder of rectal, not colonic physiology. Hypertrophy, atony and failure of sphincteric inhibition are the most reliable signposts and colonic resections will not cure them.

I should like to thank my colleagues at St Bartholomew's and St Mark's Hospitals for allowing me to review their cases.

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The classification of megacolon and megarectum that has been found useful in management, the treatment used and the results achieved, will be reviewed. Much is owed to my past chiefs and especially to Sir Denis Browne.

I regard all megacolon as secondary, as there seems to be no good evidence of a congenital primary overgrowth of the colon. The work of Swenson & Bill (1948) and of Bodian *et al.* (1949) was an important step in distinguishing the type which is now named Hirschsprung's disease. This is the megacolon secondary to congenital aganglionosis of the distal bowel. Its distinguishing feature is the hypertrophy of overactive bowel proximal to the obstruction caused by the absence of peristalsis in the abnormally innervated distal bowel. The other types of megacolon are largely characterized by a passive loading of the bowel. Table 1 summarizes the clinical contrast between Hirschsprung's disease and the other types.

Table 1
Clinical differentiation of Typical Hirschsprung's disease and rectal inertia

	Hirschsprung's disease	*Rectal inertia*
Onset	Neonatal	Training period
Constipation	+	+
Distension	+	–
Peristalsis	++	–
Rectum	Empty	Loaded
Soiling	–	+
General health	Poor	Unimpaired
Risk to life	High	Negligible

The anus in Hirschsprung's disease feels normal. In rectal inertia it is often soiled, but the sphincter usually grips normally. Occasionally one sees a patulous anus. Indeed one child was referred as having a congenitally defective anus described as being 'like an ill-fashioned colostomy'. The rocks of fæces were manually evacuated and within a week or two the sphincter tone became normal, the mucosal prolapse from ineffective straining had settled, and the anus then looked and felt normal.

The Swenson type of resection has proved sound in Hirschsprung's disease although there are still problems of management. Duhamel's (1960) operation has not yet proved its worth. Rehbein's recent follow up of cases treated by State's operation was not very encouraging (Rehbein & von Zimmermann 1960). Table 2 shows the results I have obtained during the past five years.

The group of passive megacolon is a composite one with differing ætiologies even though the radiological appearances are similar. The terminal reservoir or megarectum is the usual picture. It

Table 2
Hirschsprung's disease: personal cases 1956–1960 (Total 68)

Operation	*No.*	*Cure*	*Controlled*	*Failure*	*Death*
Swenson type	51	39	6	2	3 (+1 later death)
Duhamel	10	8	1	–	1
Nixon	2	2	–	–	–
Died before definitive treatment possible	–	–	–	–	5

Follow up over two years in 41
14 had some operation elsewhere before referral

corresponds with the clinical picture I have called rectal inertia. The colon drives the fæces into the rectum but the rectum relaxes to accommodate more and more instead of being stimulated to evacuate. A mass fills the pelvis and in severe cases reaches up to the ribs. Even in such cases observation at operation has shown that the massively distended bowel is almost all rectum and that the colon above is remarkably normal. Because flatus is passed easily, distension is not a feature, the masses are easily palpable or even visible and the general health is reasonable except in a few cases after years of neglect.

Less commonly a tubular dilatation of the distal or whole colon is seen. Its significance is still not clear. Clinically the cases seem similar. Dolichocolon is a radiological picture but I am not convinced that it has any significant anatomical basis in a congenital lengthening of the colon. The use of tannic acid in the barium enema can eliminate redundant loops or demonstrate their ability to empty effectively.

Several conditions may produce rectal inertia. The largest group appears to be that following trouble with bowel training. If training is too strict, too lax or too inconsistent the child learns to hold back the stool until the urge to defæcate passes off. If the mother fusses the child and makes an emotional and social occasion of potting then the child learns to hold back to attract attention. The painful passage of hard stools which follows the delay, frightens the child into further holding back and a vicious circle may persist until the rectum is enlarged and unable to evacuate completely even if the child wishes. Thus constipation and progressive loading of the rectum may continue long after the exciting cause has passed. Overflow incontinence may supervene and fluid motions pass around the impassable rock.

Similar events may follow some painful condition such as an anal fissure or difficult conditions such as prolonged recumbency in the treatment of orthopædic defects; or congenital deficiencies, in particular anal stenosis or neurological lesions of spina bifida or sacral agenesis. Some cases have a deeper psychological basis but in most of those of functional origin it seems to be a training problem which may have resolved years before the patient is seen – the constipation persisting because of the secondary enlargement of the rectum.

Use of the term encopresis to cover two different conditions causes confusion. That in which there is incontinence in the absence of a neurological lesion – analogous to enuresis – is probably entirely a psychiatric problem though it may be associated with some constipation and rectal loading. But overflow incontinence in severe constipation with rectal inertia (megarectum) is different. It is often due to less serious functional causes or sometimes to organic ones; though a secondary functional overlay is common in a condition which causes such social embarrassment.

Treatment of the inertia group of megacolon and megarectum is based on two principles. First that the bowel must be emptied completely and kept so, long enough to recover its tone and shrink to enable its contractions to become effective. Secondly the child must be trained to regular habitual defæcation and not allowed to wait for the call to stool. For this call is likely to be deficient, and if the child is allowed to put off defæcation then relapse is sure. One case of rectal inertia was unconscious of the inflation of an intrarectal balloon with 10 oz of fluid. After three months' treatment 2 or 3 oz caused marked discomfort. Balloon tests have not given evidence of primary abnormality of sensation except in overt neurological lesions.

The following regime has been used: (1) Manual evacuation of hard masses under general anæsthesia. (2) Daily rectal washouts – up to 20 pints of saline, a few ounces at a time. *Not* reduced when spontaneous actions begin. Minimum of two weeks, then at increasing intervals over the next four weeks or more. Hypertonic phosphate enemas or Dulcolax suppositories may be substituted after the bowel has been emptied in some cases. (3) Aperients as soon as the masses are evacuated: Senokot, Dulcolax or Mist. Neostigmin. (Follow up over many years has not revealed that regular use of aperients leads to habituation and increased need.) Aperients are withdrawn gradually. (4) *Training in regular attempts at defæcation.* This can rarely be managed at home and it is unfair to expect the district nurse to do the washouts unaided. Enemas are often useless, distressing, and sometimes dangerous or fatal. Besides water intoxication there is the risk of enema collapse – which occurs in any type of constipation with masses of impacted fæces.

Because parental ineffectuality is so often the basic cause these patients and their parents are followed up for a period of years.

Table 3 shows the results achieved – about one-third relapsing and needing further treatment but few being persistently refractory. The only death

Table 3
Megacolon and megarectum: total 46 cases (1956–1960)

Apparent ætiology	*Controlled by* Regime	Regime repeated	Operation	Failure
Management ('training')	9	2	2	1
Psychological	3	–	–	1
Anal stenosis, &c ('organic')	8	5	3	–
Precocious onset	8	–	1	1 (Died)
	28	7	6	3

Follow up over two years in 21 of the cases
2 cases not traced

was in the uncommon but interesting group of precocious, often neonatal onset.

Table 3 includes only severe cases requiring in-patient treatment. During the same period at Great Ormond Street I saw 48 cases of constipation which were less severe and were treated as out-patients. Barium enema would have shown a degree of megarectum in many of these but did not seem necessary.

A longer term follow-up is more convincing in such a condition. Eight years ago I carried out rectal sensation tests on another group of patients including 16 cases of rectal inertia. Mr J Cohen and Mr B Gampel have been able to contact 13 of these. Table 4 shows the results after eight years.

Table 4
Rectal inertia – 8-year follow up: 16 cases (13 traced)

Ætiology	*No.*	*Cured*	*Much improved*●
'Management'	7	6	1
'Psychological'	1	–	1
'Organic'	1	1	–
'Precocious'	4	3	1
	13	10	3

●Slight symptoms, insufficient to need further treatment

The results of the sensation tests are shown in Table 5. The perineal (rectal) sensation was often obtained only by a very large bolus up to 10 oz in the balloon instead of the usual 2 or 3 oz. The failure to produce more than abdominal colonic sensation in 8 is, I think, secondary to the enlargement and not due to primary neurological defect. For in the 3 which were retested after treatment rectal sensation had been restored.

Table 5
Sensation tests
(Intrarectal balloon distended with 1 oz increments of water)

5 cases: Rectal sensation normal though some to larger bolus than usual
8 cases: Colonic sensation only; of which 3 were retested after treatment and then had normal rectal sensation

Occasionally the anatomical enlargement of the rectum is such that it cannot revert to normal and relapse is inevitable. These are perhaps the ones met in adults. I have found segmental colectomy useless and have resorted to abdomino-anal resection of the rectum as for Hirschsprung's disease. There was a definite hypertrophy of the rectal wall. The operation is only a substitute for the first part of treatment. Training in regular defæcation habits is also essential – the more so as a low resection will reduce the specific rectal sensation. I think it is useless to operate until the child is old enough to co-operate in this after-care.

It is not satisfactory to resect so as to leave the 7 cm necessary for full rectal sensation because the bowel is ballooned right down to the anal canal and the retained rectal segment is sufficient to form the beginning of another megarectum. It did so in the one case in which I left some bowel. I did this because the child had a treated imperforate anus with an incomplete sphincter and I feared incontinence if I went too low. In another case I have narrowed the rectum by excising a section anteriorly instead of excising it all, because previous segmental colectomies had been carried out elsewhere. Relapse had occurred and there was no mobilizable loop of colon to bring down. It is too early to assess the result.

Less Common Types of Non-Hirschsprung Megacolon of Precocious Onset

First a rare type of which I have had two examples – one fatal. They imitated Hirschsprung's disease in infancy in many of their features, clinically and radiologically. Both babies failed to thrive. They had marked gaseous abdominal distension and constipation but visible colonic peristalsis was not prominent. The barium enema showed marked distension of the colon proximally with an undilated distal segment. Some improvement was obtained with rectal washouts. In both my cases a colostomy was performed but it was immediately evident that there was none of the colonic hypertrophy so typical of Hirschsprung's disease. The colostomies did not help. The proximal colon still did not evacuate. The first infant died with fæcal masses still in the right colon. In the second case the colostomy acted and then discharged excessive fluid. After treatment of the electrolyte disturbance the colostomy was closed and the child recovered and now progresses well. It seems that there had been a functional paralysis of the colon. Histological examination of the wall revealed no abnormality of the intramural plexuses, colitis or other abnormalities.

Dr M Bodian pointed out that the head circumference of the first case was small for her age and the brain showed cerebral atrophy. He suggested the possibility of a central origin for the abnormal

motility. The head of the second case is well below the 10th percentile also, being 15 cm at the age of 6 months.

Others of precocious onset have presented the picture of the terminal reservoir. But the history of constipation has reached back even to the neonatal period and clearly training had nothing to do with their onset. Gairdner (1960) has called this congenital constipation. Harris *et al.* (1954) has suggested that it is the result of slight anal stenosis relieved spontaneously by the passage of stools or the examining finger. Perhaps a central nervous factor should be considered for 2 of our cases had difficult births and the more florid cases of acute functional obstruction in cerebral birth trauma are well recognized.

It is tempting to consider that this syndrome might result from a very short Hirschsprung segment, so short that perhaps only the internal sphincter was involved and unable to relax in coordination with the defæcation wave of peristalsis. Biopsies have failed to show any abnormality and certainly when aganglionic segments as short as 2 cm have occurred they have presented the typical Hirschsprung symptomatology, A few internal sphincterotomies were performed in reservoir cases but the results were not impressive.

In these conditions I find it very difficult to decide what is cause and what is consequence, what is inborn and what is learned.

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Colonic Motility in Megacolon

The term megacolon indicates no more than the radiological or operative finding of a grossly enlarged colon. The diameter of the colon at barium enema, however, will depend not only on the state of the organ at the time, but also on such factors as the volume of fluid and the pressure head used together with the patient's toleration of the procedure. For this reason, it is necessary to restrict the definition to patients who have, in addition, a history of severe and prolonged constipation with or without overflow incontinence. In this study, the motility of the pelvic colon of 16 patients is described. The sigmoid colon was dilated in all 16 and all but 1 had a megarectum. Two patients had biopsy evidence of aganglionosis (of the rectal segment) and in another the clinical diagnosis was congenital megacolon. The diagnosis was confirmed at operation in 5 cases and at post-mortem in 1.

Methods and Normal Patterns

The motility of the pelvic colon was studied by three miniature balloons (7 mm diameter × 10 mm) arranged in series and recording on a metal capsule optical manometer (Rowlands *et al.* 1953). The tube was passed into the colon with the balloons in position at 25, 20 and 15 cm from the anus so that simultaneous records could be obtained from three positions. Details of the method have been published elsewhere (Connell 1961*a*).

In the normal subject the principal wave seen represents a slow contraction lasting between 20 and 30 seconds and of varying amplitude up to 100 cm of water pressure. The contractions are segmental and areas of the colon separated by 5 cm nearly always show independent activity (Fig 1). Peristalsis, recognized as a wave of contraction sweeping caudally in sequence over the three balloons, is rarely seen.

Results

Patients with megacolon demonstrate relative colonic hypomotility. It is doubtful if this group of patients is in any respect homogeneous, and motility patterns tend to support this. The motility records fall into four groups:

(1) *Generalized hypomotility:* Records in the resting state in this group show generalized hypomotility. There are occasional spontaneous waves, never of great amplitude (Fig 2). Some show low-grade activity almost continuously. This activity has no apparent propulsive purpose.

These patients were studied late in their disease and it is difficult to say whether this hypomotility represents colonic inertia or a phase of exhaustion secondary to prolonged overactivity. Two of the 7 patients had been using laxatives excessively for many years, one taking ½ lb of senna leaves a day. It seems possible that the hypomotility was secondary to excessive purgation. Another patient aged 21 had a short aganglionic segment and the colonic inertia may have been subsequent to prolonged attempts to overcome the resistance of this segment. No ætiological factors could be detected in the other patients who had a history typical of idiopathic acquired megacolon.

(2) *Colonic inco-ordination:* Three patients presented with persistent colonic activity in all three channels, but differed from normal in that the motility pattern of each segment was almost identical (Fig 3). This implied that the colon, while not inert, had been unable to develop its normal segmental activity, thus permitting the accumulation of a mass of fæces. Recording devices placed in this continuous column of fæcal material necessarily recorded identical patterns.

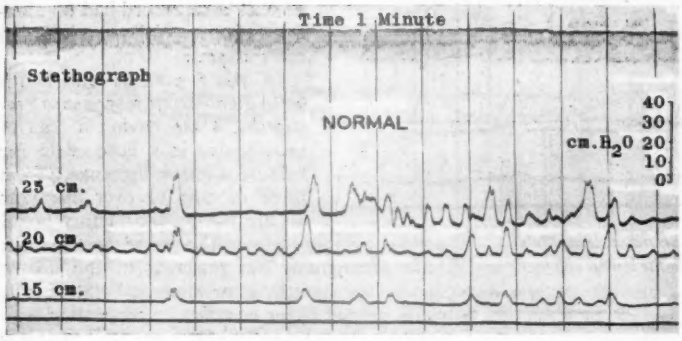

Fig 1 *Normal colonic motility showing segmental activity (reproduced from Connell 1959). In this and in all subsequent figures the lowest trace is from between 10 and 15 cm from the anus; the second from the bottom, between 15 and 20 cm from the anus; and the third from the bottom, between 20 and 25 cm from the anus. The upper trace is a respiratory record. Calibration in 10 cm steps, verticals = 1 minute in all figures*

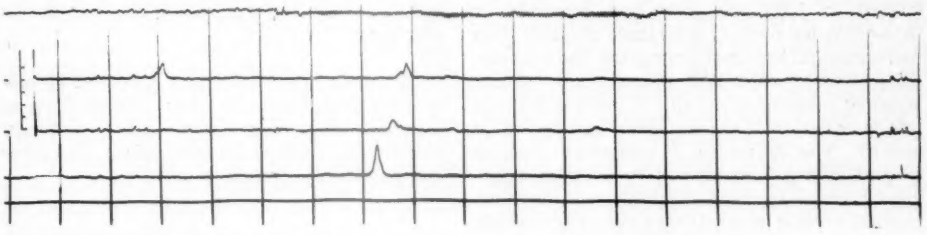

Fig 2 *Generalized hypomotility in megacolon*

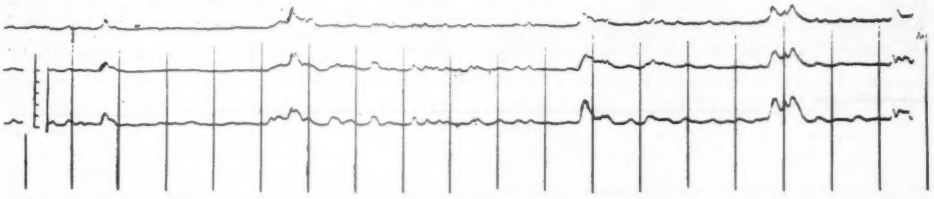

Fig 3 *Colonic inco-ordination in megacolon. The activity of each channel is similar*

Of these 3 patients one had a history typical of acquired megacolon, another, a boy of 16, had been diagnosed in childhood as Hirschsprung's disease on clinical and radiological grounds but had never had a full thickness biopsy. The third is of particular interest: she was aged 51 (a patient of Mr H Thompson's) and, following left hemiplegia, developed gross abdominal distension seen radiologically to be due to distension of the distal colon. The patient died of a myocardial infarct. A post-mortem showed that 25 cm of the descending colon was narrowed and hypertrophied but with normal mucosa; distally there was gross post-stenotic dilatation and muscular thinning of the sigmoid and rectum. Ganglion cells were seen in normal numbers in both areas of gut.

(3) *Segmental hypomotility:* A second group of 3 patients demonstrated inactivity in one segment only. Fig 4 is from a girl of 15 who was subsequently shown to have an aganglionic segment from the anus to 17 cm, although a barium enema did not reveal a constricted rectum. The lower trace is from the aganglionic segment. It is not amotile but shows low amplitude and apparently purposeless activity. The other 2 patients had different clinical histories: (*a*) A girl with acquired megacolon who had a subsequent resection of the colon which contained normal numbers of ganglion cells. (*b*) A middle-aged woman who was developing a megacolon at the same time as a progressive pyramidal lesion of all four limbs.

(4) *Normal records:* Three of the subjects had records which were normal in all respects. Each had an acquired megacolon but on crude testing 2 of the patients had grossly diminished rectal sensation without any abnormality of sigmoid sensation.

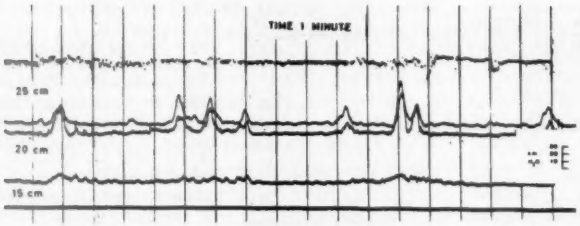

Fig 4 *Segmental hypomotility in megacolon. Only low-amplitude activity is seen in the lowest channel*

Effects of Drugs

(1) *Prostigmin*, in a dose of 0·5 mg S.C., has been studied in 7 patients. Five had depressed or inco-ordinated motility in all three channels. One had segmental hypomotility and one had an essentially normal record. With one exception all had acquired megacolon. In all but one the Prostigmin increased both the segmental and peristaltic activity. The difference is sometimes striking (Fig 5). The patient known to have an aganglionic rectal segment demonstrated the most marked increase in peristaltic waves (Fig 6) which coincided with the passage of soft fæces. Here it is probable that the Prostigmin augmented a response which was developing spontaneously. Almost certainly the recording points were above the aganglionic segment. One patient who had a normal basal record had no alteration of activity following injection of Prostigmin.

Of the 6 patients who had a good manometric response to Prostigmin, 4 are having a trial of neostigmine in a dose of 15 mg t.d.s. In a follow-up ranging from three months to over one year all are having satisfactory bowel actions on this regime. The other two did not have neostigmine but resection of the dilated bowel. Six months after surgery both patients again needed either laxatives or suppositories to achieve a satisfactory bowel action. The remaining patient who had a poor response to Prostigmin had a resection and was satisfactory four months afterwards.

(2) *Mecholyl:* Two patients, 1 a proved Hirschsprung's disease and the other suffering from an acquired megacolon, were given sufficient Mecholyl to produce systemic effects. In neither case was there alteration in motility.

Discussion

The intraluminal pressures of the colon have been determined. These represent one aspect of intestinal motility which is a term used to describe a number of different but related parameters, in-

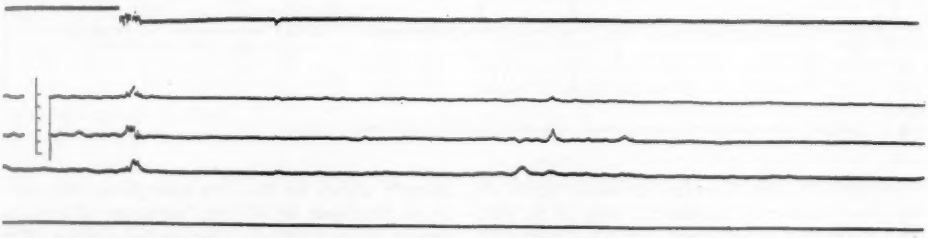

Fig 5A *Colonic activity before Prostigmin*

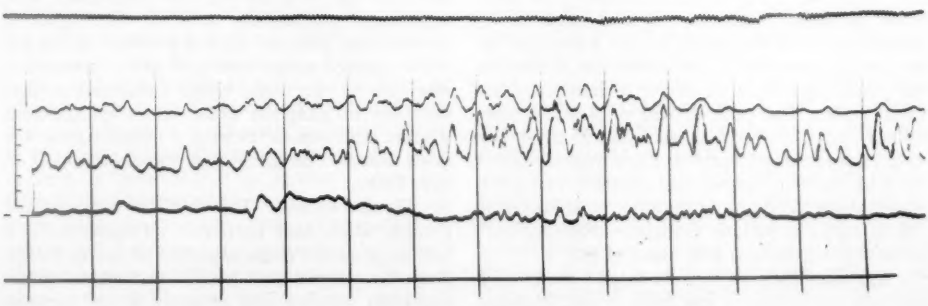

Fig 5B *Activity in same patient following 0·5 mg Prostigmin S.C.*

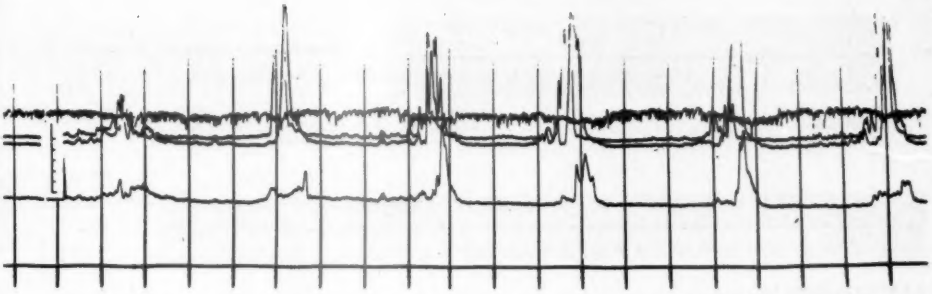

Fig 6 *Powerful peristaltic waves in patient with Hirschsprung's disease following 0·5 mg Prostigmin S.C.*

cluding transit through the bowel, the radiological or surgical appearances of bowel movements, intraluminal pressure changes, and bowel tone. In megacolon the tone of the colon is probably abnormal and information about this would be helpful; it is not possible to record the tone of smooth muscle directly in man. The other approach is to use miniature recording devices to study intraluminal pressures which reflect changes in tone although no absolute measures of tone can be made. It is often thought that the base line pressure of a motility trace is a measure of tone but this is not so as the most important component of the basal pressure is the hydrostatic pressure of the body tissue, and bowel tone appears to contribute very little to it. Understanding of the motor defect in megacolon will probably only be achieved when, in addition to measurements of intraluminal pressures, measurements of tone are also made.

These intraluminal pressures indicate that there is no defect of motor function common to all cases of megacolon. The whole group shows generalized hypomotility but there are important differences in different subjects which in this presentation have been grouped into four categories. This finding is consistent with the hypothesis that the anatomical abnormality of a megacolon may be common to a number of distinct physio-pathological processes. Generalized hypomotility and segmental inactivity have been seen in a minority of severely constipated subjects who do not have a megacolon (Connell 1961*b*). These disorders of motility may be better understood if considered functionally rather than anatomically. The anatomical abnormality may be the common end-result of a number of distinct pathological conditions such as colonic inertia, which may be either primary or secondary to excessive purgation, inco-ordinate colonic motor activity, colonic aganglionosis, and other obstructive lesions or diminished bowel sensation.

It is not possible to distinguish between colonic aganglionosis and megacolon resulting from other causes on the basis of intraluminal pressure measurements, but it has been suggested that some separation might be achieved on the basis of the colonic response to Mecholyl. Davidson *et al.* (1955) showed that in 4 of 6 patients with Hirschsprung's disease there was relaxation of the normally innervated bowel with no alteration in the motility of the denervated segments. In normal persons this differential relaxation was not seen. In the 2 patients tested with Mecholyl the results were not helpful but Davidson's observations warrant further assessment.

The disappointing results of surgery in acquired megacolon suggest medical treatment whenever possible. Although the number of patients in this series is small there was a good clinical response to Prostigmin where there had been a good manometric result. It is suggested that this Prostigmin response test is a useful guide to therapy in these patients.

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Megacolon: A Physiological Study

An experimental technique has been developed to investigate rectal physiology and provide measurable information about rectal activity, in contrast to the purely anatomical information obtained from barium enema studies.

Continuous electrical activity in the external sphincter ani has been demonstrated by electromyography (Floyd & Walls 1953). This is in marked contrast to striped muscle elsewhere (Fig 1) and is due to a continuous postural contraction which is unique in the muscles of the pelvic floor (Porter 1960).

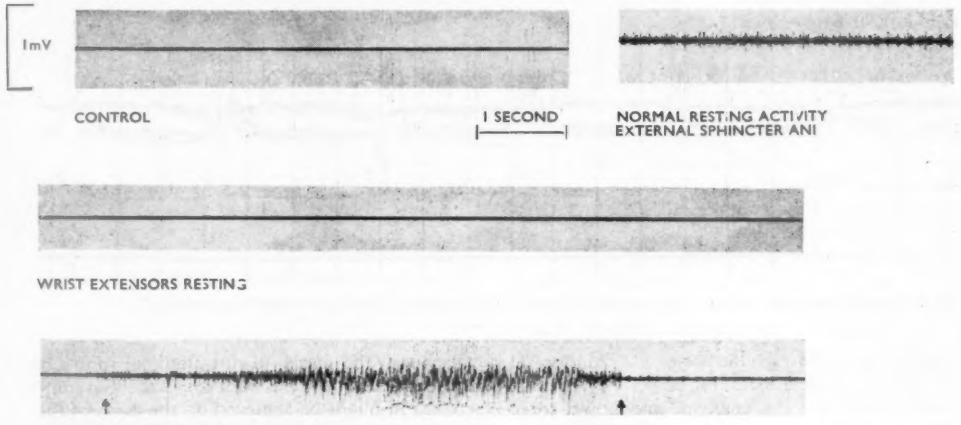


Fig 1 *The external sphincter shows continuous activity at rest. The wrist extensors are inactive unless a volitional contraction is made*

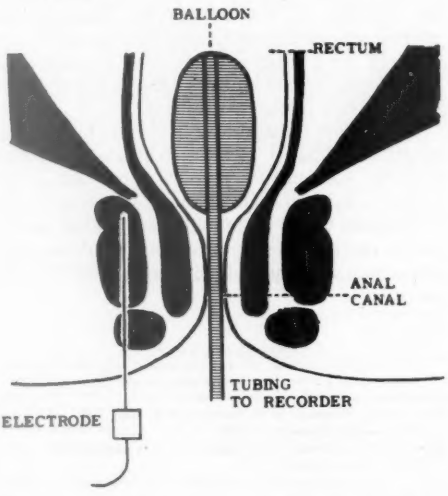


Fig 2 *A standard Miller-Abbott balloon lies in the rectum connected via a fine tube to a pressure recorder. A concentric needle electrode is inserted deeply into the external sphincter ani to record electrical activity*

This continuous electrical activity can be inhibited by rectal distension with a balloon (Fig 2), and the point at which it disappears recorded by means of needle electromyography. Inflation is carried out in 50 ml stages; initially the electromyogram (Fig 3) shows that the external sphincter is stimulated to increased activity; this is succeeded by progressive inhibition, which finally becomes complete.

Pressure changes within the balloon record the response of the rectal wall to distension (Fig 4A), which initially resists filling and then relaxes. These intrarectal pressure changes are conveniently expressed as a graph (Fig 4B).

In normal subjects rectal sensation, transient at first, always precedes inhibition of the external sphincter, which occurs with a volume of 150–200 ml, and a pressure of 45–55 mm Hg. The pattern of the rectal pressure graph (Fig 4B) is therefore constant.

In abnormalities of rectal function changes may be found in: (1) The threshold for reflex spincter inhibition. (2) The threshold for subjective rectal sensation. (3) The pattern of the rectal pressure graph.

It is worthy of note that in Hirschsprung's disease the responses to testing are normal. The sensory pathways for both conscious rectal sensation and reflex sphincter inhibition are therefore intact.

Idiopathic Megacolon

For convenience the cases of idiopathic megacolon have been classified by their radiological appearances: (1) Megarectum with a normal colon. (2) Megacolon with megarectum.

Megarectum with a normal colon: This group of patients presents early in life with a life-long history of constipation. Fæcal soiling and incontinence are common. Examination reveals a grossly loaded rectum and often a lax anal canal. The barium enema shows rectal distension with a normal colon above. Rectal biopsy is normal.

In two patients examined by the method described above the findings were grossly abnormal.

Case 1 Female, aged 17

The rectal pressure graph (Fig 5A) shows a slowly rising curve. This indicates a lax atonic rectal wall.

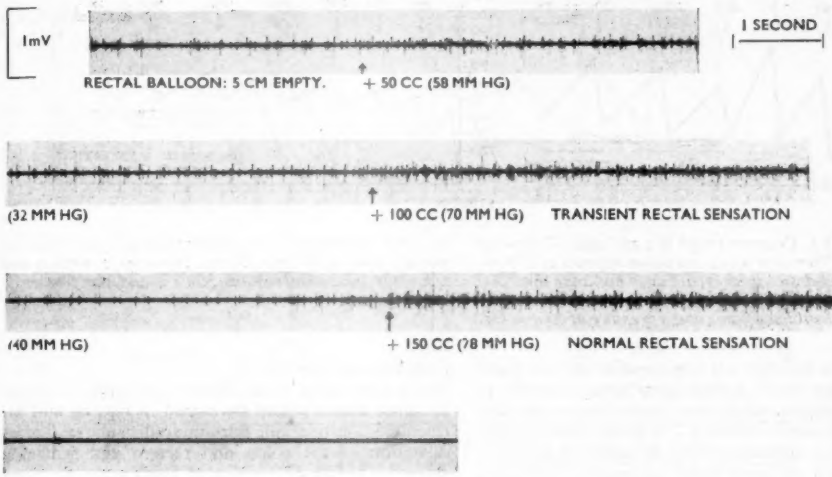


Fig 3 *Electromyogram of the external sphincter ani showing normal resting activity with an empty balloon in the rectum 5 cm from the anal verge. At each arrow 50 ml of air is injected into the balloon. This produces an increase in activity each time, which is succeeded by an increasing degree of inhibition. Inhibition is complete one minute after 150 ml has been injected. Rectal sensation precedes inhibition and increases in proportion to the degree of distension*

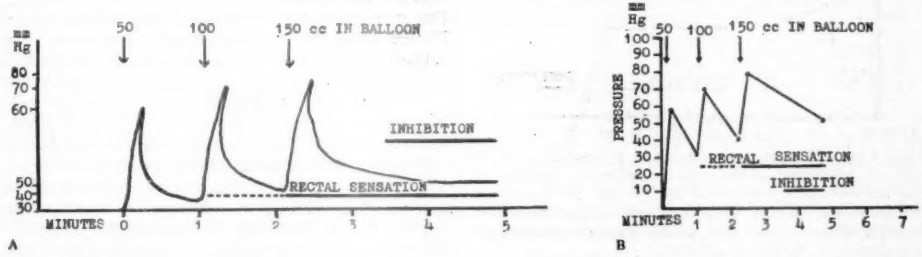


Fig 4A, *Pressure tracing recording intrarectal pressure changes in response to balloon distension in a male aged 34. At each arrow 50 ml of air is injected into the balloon. Initially the rectal wall resists distension and a peak is obtained; as the rectal wall relaxes the pressure falls to a new resting level over the course of a minute. Transient rectal sensation is represented by the broken horizontal line, the normal urge to defæcate by a solid line. Inhibition of the external anal sphincter is marked by the solid line labelled 'Inhibition'.* B, *Pressure graph expressing the pressure tracing plotted against time in minutes. It shows that the normal intrarectal pressure curve rises relatively steeply to 50 mm Hg with 150 ml in the balloon*

Rectal sensation and inhibition of the external sphincter are present, but the threshold for both is raised. The anal canal is lax.

After treatment with neostigmine for three weeks this patient had a regular bowel habit. Re-examination (Fig 5B) showed that rectal tone had improved, but the threshold for sphincter inhibition remains at a high level. Sensation is still impaired.

Case 2 Female, aged 21

This patient obtained a bowel action four times a day by means of oral Dulcolax. The signal for defæcation was abdominal colic and not rectal or perineal sensation. The rectum contained a large fæcal mass of which she was unaware and which she was unable to pass, in spite of marked anal laxity.

The electromyogram showed complete inhibition of resting activity in the external sphincter and puborectalis, undoubtedly due to fæcal distension of the rectum, which thus simulated the balloon in our experiments.

On inserting a balloon into the rectum a little continuous activity was induced in the external sphincter. This showed a slight increase with each 50 ml addition of air until 150 ml was reached, when external sphincter inhibition reappeared. In spite of this, an attempt to

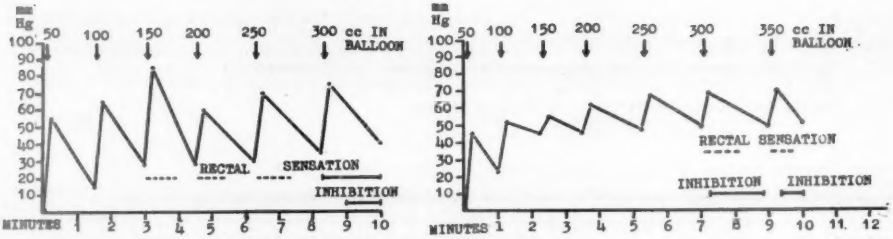


Fig 5 **Case 1** A, *Pressure graph in a girl aged 17 showing a slow rise. Transient rectal sensation appears at 150 ml, but a normal desire to defæcate does not arise until 300 ml have been added. Inhibition of the external sphincter appears at the same volume and a pressure of 40 mm Hg.* B, *After treatment with neostigmine pressure rises to normal levels with only 150 ml. However, sensation and sphincter inhibition require 300 ml and the former is only transient*

defæcate the balloon was unsuccessful and produced anal pain and spasm, with a sharp burst of activity in the anal sphincter. After removing the balloon the anal sphincter remained inhibited. The rectal pressure curve has a normal appearance (Fig 6), which is, however, superimposed on gross rectal distension. Therefore, above a certain threshold normal pressure responses and inhibition appear, but rectal sensation is grossly impaired.

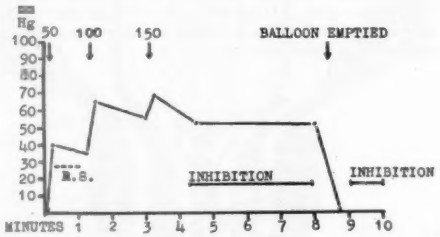


Fig 6 **Case 2** *The pressure curve rises to normal levels at 150 ml; inhibition of the external sphincter appears at this volume and a pressure of 50 mm Hg. On emptying the balloon sphincter activity returns temporarily, but is succeeded by inhibition again. Rectal sensation is transient with the first 50 ml only*

The experimental findings in these two patients are complementary. Rectal filling is hardly noticed at conscious level and sphincter inhibition requires a grossly abnormal fæcal mass. This is usually too large and hard to pass, in spite of the anal relaxation it produces. The attempt to defæcate stretches the anal canal abnormally, producing pain and spasm, and the attempt is abandoned. However, further filling above this level can initiate partial defæcation provided the fæces are soft. If, on the other hand, they are liquid the patient is incontinent as the external sphincter is already inhibited and rectal sensation is impaired.

Megacolon and megarectum: Two patients examined in this group provide a striking contrast physiologically, in spite of a similarity in their clinical histories and barium enema studies.

Case 3 Female, aged 36

This patient had a normal bowel habit until the age of 25, since then she had developed increasing and intractable constipation. Barium studies showed gross dilatation of the colon and rectum and screening showed pooling of barium in the cæcum for long periods.

The rectal pressure graph (Fig 7A) shows an extraordinary degree of rectal atony. The inhibitory threshold is enormously raised and rectal sensation is absent. Neostigmine produced neither significant rectal contraction nor clinical improvement.

Case 4 Male, aged 39

This man had a normal bowel habit until the age of 33. He then became increasingly constipated. The barium enema showed a similar degree of dilatation to that in the previous case, but no pooling in the cæcum.

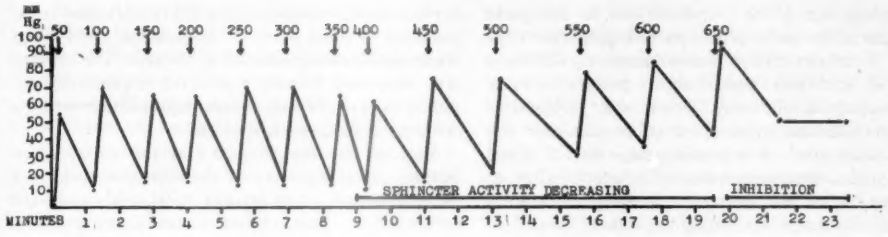
The rectal pressure graph (Fig 7B) provides a striking contrast to that in Case 3. The rectum is hypertonic and hyperactive. The rectal sensory threshold is low and that for sphincter inhibition is normal.

Neostigmine restored this patient's bowel habit to normal. It is difficult to reconcile the experimental findings in this case with the radiological picture of megacolon. They are unlike our findings in any other patients in this series.

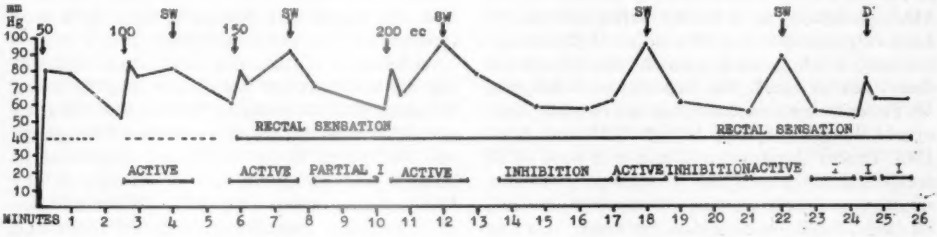
Discussion

The rectal pressure graph provides an objective index of rectal muscle function provided it is related to inhibition of the external sphincter, rather than subjective rectal sensation which is variable and sometimes absent. The response to treatment can be gauged from a series of graphs. Neostigmine may convert the rectal pressure curve to a normal pattern.

Eight of the patients investigated were treated with neostigmine; in one of them with extreme atony it failed to produce clinical improvement. It appears to act by improving peristalsis and increasing rectal tone. There is no evidence that it reduces the threshold for inhibition of the external sphincter when this is high.



A



B

Fig 7A, **Case 3** *Intrarectal pressure fails to rise until 400 ml has been injected. Thereafter it rises slowly with increasing sphincter inhibition. This becomes complete at 650 ml and 50 mm Hg pressure. Rectal sensation is absent.* B, **Case 4** *Pressure rises steeply with only 50 ml; transient sensation appears at this volume. Above 100 ml rectal filling evokes rectal contractions: 'SW'. A normal urge to defæcate is experienced at 150 ml and inhibition is complete at 200 ml, though this is interrupted by each rectal contraction, but returns as the rectal wall relaxes once more. At 'D' the patient attempted to defæcate the balloon but failed, in spite of inhibiting the external sphincter on bearing down*

It is apparent that no constant pattern of behaviour in patients with idiopathic megacolon has been forthcoming from this study. This must be a stimulus to further research on a tantalizing problem.

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Megacolon and Megarectum in Chagas' Disease[1]

The object of this paper is to present the results of the surgical treatment of megacolon and megarectum in Brazil and a summary of recent contributions by Brazilian authors which have brought about a better ætiological and physiopathological knowledge of the disease. This presentation is an account of work carried out in the Medical School of Ribeirão Prêto.

[1]Enquiries regarding this paper, including requests for reprints, should be addressed to Dr Basil C Morson, Research Department, St Mark's Hospital, City Road, London, E.C.1

Nomenclature

Numerous eponyms have been proposed for the condition. Obviously 'idiopathic dilatation' had to be abandoned as soon as the pathogenesis of the disease was more clearly understood. 'Achalasia of the colonic sphincters' is not sound, since the existence of such sphincters, both from the anatomical and from the functional standpoint, is questionable. According to our clinical and surgical experience, no achalasic zone or ring has been found distal to the dilatation of the sigmoid colon or rectum. The terms 'megacolon' and 'megarectum' are acceptable on a roughly descriptive basis and because of tradition inasmuch as they refer to the colonic and rectal dilatation which constitutes an advanced stage of the disease. In early stages of this disease patients have a functional abnormality without dilatation of the intestine, and for this reason the terms megacolon and megarectum are not accurate.

According to our present knowledge of the disease, the better name is 'aperistalsis' of the colon and/or rectum. This term was suggested by Brasil (1955) for a similar condition occurring in the œsophagus and was extrapolated for the disease of the large bowel. It was officially recommended by the Brazilian Federation of Gastro-

enterology in 1959. 'Aperistalsis' is adequate because of its good physiopathological connotation: it means motor inco-ordination, defective motility, and disturbed or absent peristalsis without propulsive efficiency. This is what happens in the so-called acquired form of megacolon: the fæcal stagnation is a consequence not of distal mechanical obstruction but of a functional inco-ordination of the muscular activity in a long intestinal segment including the dilated bowel.

Incidence

A partial survey of the autopsy records in the Medical School at Ribeirão Prêto showed 69 cases of megacolon out of a series of 556 autopsies not including casualty deaths nor infants less than 1 year of age. In the Department of Surgery, 58 patients with rectocolonic aperistalsis were operated upon between March 1955 and April 1961. In this Department 4 beds in a ward of 30 are permanently occupied by such patients. If a selective policy for admissions were not adopted, all beds could be occupied by them and by those with aperistalsis of other hollow viscera, especially the œsophagus. This is a reflection of the high prevalence of the disease in Brazil, especially in the central areas.

In Brazil the geographical areas in which cases of aperistalsis are observed closely coincide with those where Chagas' disease (*Trypanosomiasis americana*) is endemic, and the majority of patients with megacolon and megarectum present the immunological characteristics and the electrocardiographic patterns of chronic Chagas' disease. Similar observations have been made recently in Chile (Atias *et al.* 1959) and Argentina (Rosenbaum & Cerisola 1958). There are reasons for believing that a methodical investigation of œsophageal and bowel dynamics in other countries in which Chagas' disease is known or has been observed (South and Central America and the Southern part of North America) would disclose a similar relationship.

Mega-œsophagus and megacolon, as segmental dilatations of the alimentary canal, are advanced pathological phases of a systemic disease and frequently occur together. In the above-mentioned autopsy series, there were 62 cases with mega-œsophagus of which 31 (50%) also had megacolon; out of 69 cases with megacolon 19 (27·5%) also had mega-œsophagus. In our series of 58 surgical patients with aperistalsis of the colon and rectum, 48 have had radiological examination of the œsophagus: 23 (47·9%) showed œsophageal aperistalsis and most of them had degrees of dilatation (mega-œsophagus). Recent investigations with myographic recordings (Vieira & Godoy 1961, personal communication; Vieira, Godoy & Carril 1961, personal communication) revealed a typical positive response by the œsophageal musculature in most cases of megacolon, even when there was no complaint of dysphagia. The reverse was observed, namely a positive response by the colon in cases of mega-œsophagus, either with or without obvious constipation.

Besides the œsophagus and the distal large bowel, other segments of the digestive tract and other hollow viscera present aperistalsis and may eventually become dilated. In this autopsy series, there were 5 instances of megagastrum, 2 of megaduodenum, 1 of megajejunum and 2 of megavesicula (dilatation of the gall-bladder). We have also seen megaureter. Similar findings have been reported by Etzel (1942) and Raia (1943).

Aperistalsis of the colon and rectum occurs at any age and in either sex. In our surgical series, the oldest and the youngest patients were 64 years and 10 months old respectively. The average age was 34·7 years. In our experience megacolon in infancy and childhood is not always of the Hirschsprung type. We have observed two children with 'megacolon': one of them had microrectum, diaphragmatic occlusion of the sigmoidorectal junction and dilatation of the left colon; the other, 10 months old, had megacolon and megarectum. Pathological studies have confirmed that the first had Hirschsprung's disease and the latter Chagasic aperistalsis.

No special study was made of race or occupation, but the majority of the patients come from rural districts. Similar observations were published by Freitas Jr. (1950) and Rezende (1956).

Pathology

Since the third decade of this century, when degenerative and inflammatory lesions in the myenteric plexuses were first described (Hurst 1925, 1934, Etzel 1937), there have been many contradictory ætiological theories, but there is unanimity in ascribing an important role to the destruction of the ganglion cells as the causative mechanism of œsophageal or colonic dysfunction and dilatation. Some authors, quoted by Cutait (1953) and Raia (1955), describe a distal aganglionic segment in all cases of megacolon. According to them, there is a functionally strictured distal segment, the rectum, in which the ganglion cells are absent, in contrast to the proximal dilated sigmoidal loop, in which they are present. This is true for Hirschsprung's disease, but in our experience at Ribeirão Prêto this is not true of aperistalsis or acquired megacolon and megarectum. In these there is a reduction in the number of ganglion cells throughout both the rectum and the colon. Moreover the quantitative reduction of the ganglion cells is observed in all segments of the alimentary tract, with the eventual appearance of other enteromegalic segments, especially in the

œsophagus (Amorim & Corrêa Netto 1932, Köberle & Penha 1959).

The conflicting findings and interpretations of the histopathological features of 'aperistalsis' are understandable and have a possible explanation in the following facts: (1) Most pathologists concentrate on the qualitative changes in the myenteric plexuses and do not pay attention to quantitative analysis. (2) The samples submitted to microscopic examination are not representative. As a rule, the specimen is either a small fragment taken arbitrarily from any part of the surgical or autopsy specimen, or a thin strip of the muscular layer of the sigmoidorectal junction or the œsophageal cardia obtained during a non-excisional operation, as, for example, the pelvirectal sphincterotomy (Corrêa Netto's procedure) and the gastro-œsophageal extramucosal myotomy of Heller. With such sampling, normal and abnormal nerves may be found or none at all. The result is inconsistent and inconclusive.

Köberle (1956, 1959*a*, *b*) and his assistants at Ribeirão Prêto have performed a quantitative analysis of the ganglion cells in serial sections of many blocks of various representative tissue fragments taken from each surgical or autopsy specimen. Ring segments 1 mm high of the circumference of the intestine and œsophagus, with serial sections from each ring, showed the following average numbers of ganglion cells.

For the colon and rectum, at various levels:

	Cæcum	*Transverse*	*Sigmoid*	*Rectum*
Normal	4,163	4,947	5,785	4,036
Megacolon	189	253	381	163
Percentage of normal	4	5	6	4

For the œsophagus, at three different levels:

	Upper	*Mid*	*Lower*
Normal	445	778	1,003
Chagas' disease with apparently normal œsophagus	122	261	391
Mega-œsophagus	0·1	1·5	2·7

This striking reduction of the ganglion cells has been consistently found in our specimens of the colon and rectum (Köberle 1956, 1957) as well as for the œsophagus (Köberle & Penha 1959). It is also observed in the heart (Alcantara 1959) and, but less markedly, in the remaining segments of the digestive canal and in the wall of other hollow viscera, e.g. the biliary ducts, the ureters, and the bronchi (Köberle 1959*b*).

The partial or complete aganglionosis of the œsophagus and of the colon was formerly ascribed to a nutritional deficiency of vitamin B_1 (Etzel 1935). But Chagas (Chagas 1916, Chagas & Villela 1922), in his original descriptions of the disease, pointed out the frequent finding of enteromegalies and suggested that the *Trypanosoma cruzi* could be responsible for them. Other Brazilian authors have emphasized the similar geographical distribution of Chagas' disease[1] and the enteromegalies as well as the high incidence of positive complement-fixation tests for *T. cruzi* in patients with mega-disease. Mayer & Rocha-Lima (1914) reported the finding of the parasite in the stomach wall of monkeys and Köberle & Nador (1956) presented further morphological support for this ætiological relationship by showing that the muscular fibres of the hollow organs harboured pseudocysts of the parasite in the leishmania phase: the pseudocysts rupture, causing an inflammatory reaction in the tissues between the two muscular layers with partial or complete destruction of the ganglion cells. Köberle and his co-workers also demonstrated, in human Chagas' disease and in rats inoculated with *Trypanosoma cruzi*, that the quantitative and qualitative changes of the nerve cells occur not only in the intestine but also in the heart (Alcantara 1959), in the bronchi (Köberle 1959*b*) and in the spinal cord (Schwartzburd & Köberle 1959). Köberle (1956) suggests that a neurotoxin liberated after the rupture of the pseudocysts and the disintegration of the leishmania forms of the *Trypanosoma cruzi* is the cause of the degenerative changes in the ganglion cells.

Other toxic factors may be responsible for such lesions and for aperistalsis under certain special conditions and in the countries where Chagas' disease does not occur. Worms & Leroux-Robert (1934) ascribed the ætiology of some cases observed in France after World War I to gas poisoning (Yperite). And Erwenich (1940) suspected that the ganglion cell destruction was caused by diphtheria toxin.

In South America, however, aperistalsis and enteromegaly are a manifestation of Chagas' disease. In Ribeirão Prêto we believe that this will be soon confirmed in other areas. The papers

[1]The *Trypanosoma cruzi* is the causative agent of Chagas' disease and is transmitted to man by blood-sucking insects belonging to the subfamily triatominæ. When the infected insects bite an individual there may be contamination of the wound by the insect's fæces, which contain numerous parasites. The vector chiefly bites the face and this is the reason for the nickname 'barbeiros' (barbers). There is multiplication of the trypanosome at the point of the initial infection. A few days later, the parasites disappear from the blood stream and invade smooth muscles and the myocardium. They multiply in these tissues in the form of leishmania and cause destruction of the adjoining tissue with the formation of cyst-like cavities. When these pseudocysts rupture, most of the leishmania are destroyed by the natural defences of the body but some of them reappear in the circulation. This cycle is repeated many times during the first weeks of this acute phase of the disease, during which diagnosis can be confirmed by direct examination of blood smears or by means of the 'xenodiagnosis', that is, allowing a laboratory-bred insect to bite the patient with examination of fæces ten days after. The symptoms are those of an acute infection, with fever, generalized adenopathy and a slight enlargement of the liver and spleen. Moreover, there is cardiomegaly with arrhythmia. About 10% of the patients die. The patients who survive go into the chronic phase of Chagas' disease which is mainly characterized by heart block, also dysfunction and dilatation of many hollow viscera. During this phase diagnosis can be confirmed by a complement-fixation test (the Machado-Guerreiro's test). Up to the present time no specific treatment for acute or chronic Chagas disease has been discovered.

by Verbrycke (1920), Vinson (1947), Templeton (1948), Emert (1952) and Bates (1952) on mega-œsophagus and megacolon, and those by Packchanian (1939) and Woody & Woody (1955) on trypanosomiasis seem to foretell this, since they come from or refer to the same geographical areas – the southern part of the United States. A few months ago Ingelfinger reported to Freitas (1960, personal communication) 4 patients with œsophageal aperistalsis observed in Boston, Mass. All had lived in the Southern States and one presented the same electrocardiographic pattern described in South American Chagasic patients. It seems desirable that every person with a positive complement-fixation (Machado-Guerreiro) test be submitted to a thorough radiological study of the œsophagus and of the large bowel. Moreover, every patient with rectocolonic or œsophageal aperistalsis should be investigated by ecologic anamnesi and a Machado-Guerreiro test (Freitas 1947).

The results of the latter in the Ribeirão Prêto series are quite impressive. The complement fixation was positive in 96·7% of the autopsy cases with enteromegaly and in 90% and 94·4% of the surgically treated cases of œsophageal and rectocolonic aperistalsis.

Another fact which favours the Chagasic ætiology of mega-œsophagus, megacolon and megarectum in Brazil is the observation made by Rezende & Rassi (1958) that, three to twelve months after the acute phase of Chagas' disease, the œsophagus, previously normal at fluoroscopy, shows radiological features of motor inco-ordination and dilatation, with the corresponding complaint of dysphagia. In 1950, similar findings were made by Nunan *et al.* (1952) in 13 children with megacolon and a previous diagnosis of acute Chagas' disease.

In 1959 Guimarães & Miranda described mega-œsophagus with leishmania in the organ wall in a rhesus monkey inoculated ten years before with *Trypanosoma cruzi*. Okumura (1960, personal communication), in São Paulo, has claimed the production of megacolon and mega-œsophagus in animals (dogs and mice) with experimental Chagas' infection.

The *Trypanosoma cruzi* is a parasite of muscular tissue but damages the ganglion cells, possibly through a neurotropic toxin. During the acute phase of Chagas' disease parasitic metastatic implants take place in variable degrees of intensity and frequency and with a variable topographical distribution. There is a local inflammatory reaction, formation of granulomas and the rupture of the pseudocysts with interstitial inflammation and toxic destruction of ganglion cells, the numbers of those destroyed depending on the intensity of the infestation. This accounts for the variability of the qualitative and quantitative morphologic features in a casual single small piece of tissue obtained in the chronic phase of the disease: whether there is further ganglion cell damage during this period is doubtful and merits further investigation.

The motor dysfunction is a consequence of ganglion cell destruction and denervation. Denervated muscular tissue, including the muscular tissue of the œsophagus and colon, when partially or totally deprived of its nervous control, becomes hypersensitive. Kramer & Ingelfinger (1951), with Mecholyl stimulation of the œsophageal musculature, demonstrated this hypersensitive response in cases of so-called 'cardiospasm'. With kimographic recordings of intraluminal pressure variations at various levels, our group in Ribeirão Prêto showed hypertonus and increased contractility after Mecholyl stimulation in Chagasic patients either with or without dysphagia as well as actual dilatation of the œsophagus (Vieira & Godoy 1961, personal communication). Our group has obtained a similar pattern in the large bowel, either with or without megacolon and megarectum (Vieira, Godoy & Carril 1961, personal communication). The colon reacts less intensely than the œsophagus to similar doses of Mecholyl and we do not know yet whether such a difference can be attributed either to the relatively less extensive neuronal destruction in the wall of the large bowel compared with the œsophagus or to a greater local production of cholinesterase in the former, as suggested by Fink & Friedman (1960). According to these findings, the hyperreactive Mecholyl test can be considered as an objective demonstration of the enteric motor dysfunction in Chagas' disease. The fact that the response has been obtained at various levels and even in the early and in the mild forms of the disease suggests that the neuronal degeneration and the corresponding motor inco-ordination are diffuse from the beginning of the disease.

The first dysfunctional stage is, therefore, hypertonus and hypercontractility, with or without clinical manifestations, depending on the degree of neuronal destruction and of the consequent motor inco-ordination (aperistalsis). This inco-ordination can be witnessed by fluoroscopy or during surgical exploration, and appears as scattered, arrhythmic, localized rings of contraction without any order or peristaltic efficiency. It is easier to see this in the œsophagus than in the colon or rectum.

As a result of motor inco-ordination and exaggerated reactivity, muscular hypertrophy soon follows. The muscular wall, although hypertrophied, has no propulsive effectiveness and there is stoppage of the intestinal content with

progressive dilatation and elongation of the loop (dolichomegacolon). This means stretching and mechanical stimulation of the muscular fibres, with the consequent additional hypertrophy, especially of the circular layer. The stagnant fæces are progressively desiccated and hardened (fæcaloma), leading to mucosal inflammation, ulcers and perforation.[1] In our surgical specimens of the dilated rectosigmoid we found no other lesions than inflammatory reaction and stasis ulceration. One patient with advanced aperistalsis of the colon and œsophagus died from peritonitis due to perforation of an ulcer in the sigmoid colon. Another complication of megacolon is acute volvulus, with or without interruption of the blood supply to the twisted sigmoidal loop. The tendency to volvulus is caused by tremendous elongation of the sigmoid colon with a characteristic thickening and retraction of the mesenteric tissues, probably a result of lymphangitis.

Two points merit discussion:

(1) Why is enteromegaly more often seen in the rectosigmoid and œsophagus, when the destruction of the ganglion cells is observed throughout the digestive tract? A possible explanation is that these two segments are more exposed to mechanical stress, since they receive and contain respectively the desiccated fæcal bolus and undigested food. The content of the remaining segments of the alimentary tube is more fluid. Mechanical burden is important. After proximal colostomy is performed, the resting 'megaloop' undergoes a striking regression. Similarly development of Chagasic cardiomegaly depends not only on cardiac denervation, but also on the work imposed upon the heart.

(2) Is there an achalasic or a strictured distal segment? Our experience gives no support to the theory of sphincteric achalasia of the rectum and of the colon. We have never found a real organic or functional distal stricture. In Hirschsprung's disease, it seems to be true that the aganglionic distal segment is functionally strictured. In Chagasic rectocolonic aperistalsis this is not found. We believe that the apparently narrow distal segment seen radiologically corresponds to the terminal part of the rectum that cannot dilate because dilatation is hindered by the neighbouring structures, particularly the pelvic musculature. For the distal œsophagus, a similar role is played by the ring and crura of the diaphragmatic hiatus.

Clinical Features

The outstanding symptom of aperistalsis of the colon and rectum is chronic constipation. Bowel movements occur with an interval of eight days to five months and must be induced by laxatives and enemata. The patient's tolerance to such prolonged constipation is astonishing. The lodged fæcaloma sometimes requires manual evacuation under anæsthesia (twenty-eight times in our series). It is often easily palpable through the abdominal wall. Rectal palpation detects dilatation and the impacted bolus. Malnutrition is a consequence either of anorexia and bad habits or of concomitant œsophageal involvement. In the latter case, there is a dysphagic complaint.

The chronic intestinal constipation is well tolerated. It becomes acute if a volvulus of the sigmoid colon complicates the picture. The diagnosis of the latter is straightforward. On six occasions (10·3%) acute volvulus caused admission to hospital, and in 2 patients there was a history of this complication.

X-ray studies are performed by barium enema, after removal of the fæcaloma. Fluoroscopic evaluation is made and films are taken before and after spontaneous evacuation. Contractility, tonus, motor co-ordination and emptying efficiency are evaluated. There is no indication for rectoscopic examination for either diagnosis or treatment, except in the special case of partial volvulus. For decompression, a tube is passed beyond the twisted rectosigmoidal junction.

It is worth emphasizing that the patients with Chagasic aperistalsis of the colon and rectum may have not only œsophageal involvement but also (1) dilatation of other segments of the digestive and urinary tract and the corresponding symptoms, (2) a cardiac condition (Ferreira-Santos *et al.* 1959), and (3) hypertrophy of the salivary glands (Vieira 1958).

Treatment

There is no curative treatment for 'aperistalsis' because the fundamental lesion, namely the destruction of ganglion cells, is permanent. Treatment is palliative, and recurrence after surgical treatment depends on the amount of damage to ganglion cells in the remaining intestine.

Lumbar sympathectomy, splanchnicectomy and pelvirectal sphincterotomy were used in the past for treating aperistalsis of the colon and rectum, but almost invariably failed. The present knowledge of the pathogenesis of the disease does not offer a sound basis for operation. Resection of the presumptive neurovegetative supply to the dilated loop increases the pre-existing intramural denervation. The external incision of the pelvirectal (Corrêa Netto 1934) and internal anal sphincters is as incomplete as Heller's operation for advanced mega-œsophagus. For many years Brazilian surgeons, including the

[1] In the œsophagus, the stagnation of food causes stasis œsophagitis, ulcers, bleeding, leucoplasia, diverticula, fistulæ and, eventually, carcinoma.

author, performed this sphincterotomy. Recurrence was the rule.

The best therapeutic approach to the problem is rectosigmoidectomy (Cutait 1953, Raia 1955, Ferreira-Santos 1959). The resection includes the dilated sigmoid and rectum with the exception of the distal 4–5 cm of the latter. Sigmoidectomy is unsatisfactory and leads to recurrence with dilatation of the left colon now anastomosed to the untouched aperistaltic rectum (Finochietto 1927, Riveros 1940). It is important to remove the entire denervated segments showing motor dysfunction, muscular hypertrophy, dystonia and dilatation, i.e. the part of the denervated intestine which has continuously endured the traumatic action of desiccated solid fæces. Even so recurrence sometimes occurs. At operation the surgeon cannot know the intensity and extension of the quantitative neuronal reduction in the remaining colonic segments.

The method used to complete the anastomosis is a matter of personal taste. Our experience includes:

Internal anal sphincterotomy		1
Right hemicolectomy		1
Left hemicolectomy		1
Total colectomy		1
Abdomino-perineal rectosigmoidectomy:		5
With Swenson's perineal anastomosis	3	
Intra-sphincteric pull-through operation	1	
Endo-anal pull-through operation	1	
Anterior suprapubic rectosigmoidectomy:		49
As the single operation	45	
The same plus anal sphincterotomy	4	
Total		58

Rectosigmoidectomy has been used more frequently for obvious reasons. Other colonic segments are resected when dilated, but this is exceptional. There are cases with total megacolon. Whether it is advisable or not to perform a total colectomy remains a controversial matter. In one case a total colectomy with ileoproctostomy was carried out, leaving behind almost the entire rectum, so that the latter would act as a reservoir and avoid the disadvantages of perineal ileostomy. The patient is doing well after more than two years, with two or three bowel movements a day. The prognosis is not good, however, as the patient had mega-ileum at the time of his operation. The second case is more recent, was submitted to a conventional anterior rectosigmoidal resection and is under observation.

When rectosigmoidectomy is contemplated, the anterior suprapubic procedure is preferred for all cases except young children. In these the Swenson technique is easier.

To avoid post-operative complications, an important point is to perform a three-staged operation, with primary colostomy of the transverse colon as the first step. Before the adoption of this policy dehiscence was frequent. Nine out of 18 anastomoses (50%) were complicated by fistula formation on the fourth post-operative day: all but one were treated by temporary colostomy, 2 had to be drained through the perineum and 4 which developed stenosis were submitted to a plastic re-operation. After a decision to perform an external stoma in the transverse colon as the first operative stage, the incidence of fistula after the second stage (resection and anastomosis) became lower: in a series of 34 consecutive resections, there were 4 cases of dehiscence, only 2 with complete fistula. None developed stenosis and healing was spontaneous. As a rule, the patient is discharged after eight or nine days, but a third stage, to close the colostomy, is required after four weeks.

When treating rectocolonic aperistalsis, the conventional measures of pre-operative bowel sterilization are not enough, whether using sulfa drugs or broad spectrum antibiotics or both. These are effective in cases of cancer or other diseases, but do not sterilize most cases of megacolon because of aperistalsis and stagnation. Of the utmost importance, therefore, is the mechanical cleansing of the colon by means of daily water enemas carrying the drugs for intestinal antisepsis through the rectum and through the distal colostomy. Seven to twelve days must elapse between the first and the second stage, and this will not be possible unless the distal gut is cleared of fæces.

In acute volvulus, there are two procedures. If no vascular damage is observed during laparotomy, operation will consist of untwisting the loop and transverse colostomy. Resection is delayed until bowel preparation is complete. In cases with necrosis of the twisted sigmoidal loop, resection is performed with double lumen sigmoidostomy. Resection of the rectum is done as a second stage, after sterilization.

Two technical details concerning rectosigmoidectomy should be mentioned. First, when a good end-to-end anastomosis is not possible because of a great difference between the diameter of the rectal stump and the descending colon, it is advisable to close the latter and to perform a side-to-end anastomosis. In 49 anterior resections of the rectosigmoid, this reconstruction was done on 8 occasions. The second point is the failure of the stumps to come together without tension, even after ligature and section of the inferior mesenteric vessels. In such a case an isolated ileal loop has been successfully interposed between the descending colon and the rectum.

In 58 operation cases there were no deaths. Follow-up studies were obtained in a few up to five years; 3 have constipation again with radiological demonstration of recurrent megaformation. The majority of the patients were operated upon in the last two years. Follow-up was

obtained in 70%: these are doing well with daily bowel movements.

Acknowledgments: I wish to record my thanks to all my colleagues in the Medical School of Ribeirão Prêto whose team-work made this investigation possible, but especially Professor Fritz Köberle, Professor J L Pedreira de Freitas and Dr Clovis B Vieira; also to Mr Ian Todd and Dr Basil Morson for their help with this lecture.

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Professor J C Goligher (*Leeds*)

I propose to confine my remarks to the two common forms of megacolon, namely Hirschsprung's disease and rectal inertia—especially the latter. For, since the brilliant pioneer work of Swenson & Bill (1948) and Bodian, Stephens & Ward (1949), there has been a not unnatural tendency in writings on the subject of megacolon to dwell on the rationale, technique, and for the most part satisfactory results of the Swenson type of operation for Hirschsprung's disease, and to dismiss rectal inertia in brief paragraphs, glossing over the lack of real insight into the condition and the unsatisfactory nature of its treatment. This is regrettable, more particularly as rectal inertia is, in my experience, commoner than Hirschsprung's. Thus of my 24 cases with megacolon only 4 suffered from Hirschsprung's disease, but 16 were examples of rectal inertia.

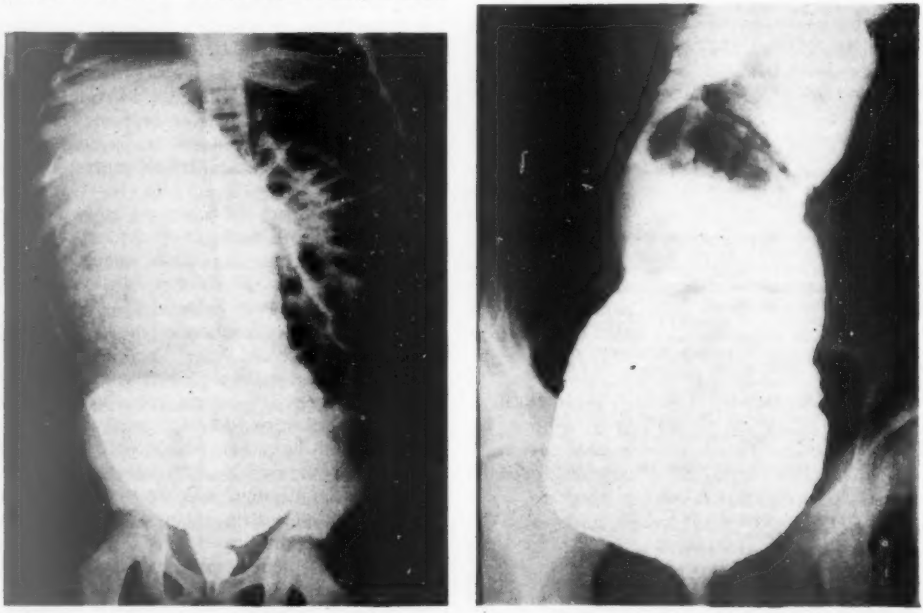
The first issue to be settled when a surgeon is faced with a case of megarectum and megacolon is to decide which of these two conditions he is dealing with. In some instances the diagnosis may be clinically and radiologically evident, as for example when the barium enema plate shows an appearance such as that revealed in Fig 1A, with a relatively contracted lower segment typical of Hirschsprung's disease, or alternatively as in Fig 1B where an enormous dilatation of the rectal ampulla extends down to the ano-rectal ring, suggesting that the condition is one of so-called rectal inertia. However, we have been assured by many authorities that the latter radiological appearance may not be incompatible with Hirschsprung's disease, when the aganglionic segment is exceptionally short, and for that reason we have usually done rectal biopsies on these cases, as recommended by Swenson (1958). But I must admit that so far we have not succeeded in uncovering any examples of Hirschsprung's disease, and I wonder how often Mr Nixon in his considerable experience has salvaged by rectal biopsy patients with aganglionic megacolon who had been relegated by the radiologist to the diagnostic 'dump heap' of idiopathic megacolon. Also I should be grateful if he would enlighten us on his technique of rectal biopsy. In theory it would seem essential to remove a portion of the rectal wall comprising both layers of the muscle coat in order to secure a specimen of the area in which Auerbach's plexus resides, but I understand that Mr Nixon normally contents himself with a mucosal biopsy. Is this really adequate, and does it give the pathologist a chance to express an opinion on the presence or absence of the essential ganglion cells?

In the management of cases of rectal inertia we have been much influenced by the teaching of the Hospital for Sick Children in Great Ormond

Street, and have usually employed the sort of conservative regime outlined by Mr Nixon. It is, however, a tedious business which does not seem to give much joy to anyone, least of all to the nursing staff, but in many cases it does enable the patients to avoid the extremes of fæcal impaction and incontinence that have usually been the symptoms bringing them to hospital in the first instance. What has been disappointing to me about this method has been the rarity of any substantial return of the rectal calibre to normal on objective examination. Even after several years the rectum is often found on palpation to contain an abnormally large accumulation of fæces, and the barium enema plates frequently show little or no diminution in the width of the rectal ampulla. However, this may be an indictment of our inadequacies in carrying out the regime. I should be interested to learn more of the objective results in Mr Nixon's cases. He did say that a considerable proportion of his patients were cured and many others much improved, but does this mean subjective or objective improvement?

In my mind, this failure to achieve a restoration of the bowel calibre to normal throws doubt on the whole idea underlying this conservative treatment – namely that the condition is due simply to habitual overdistension of the rectum from faulty bowel habits – and inclines me to the view that there is some intrinsic rectal abnormality in these cases. This is suggested particularly in those with a really enormous distension of the rectum extending into the upper abdomen. It is hard to believe that this can become normal again. A further fact pointing to an intrinsic abnormality is the finding – seldom emphasized in standard texts – that in many of these cases of idiopathic megarectum (actually 50% of my cases) there is an associated deformity of the anal region, usually an ectopic vaginal positioning of the anus. It may be objected that this is associated with anal stenosis and that the megarectum is secondary to this state of affairs. But this is not my experience; usually the ectopic anus is patulous, even more so in 2 of our 8 cases with combined megarectum and ectopia in which a 'back-cut' operation had been previously performed soon after birth.

The external sphincter in these cases with ectopic vaginal anus remains in the perineum, so that the anal orifice has no surround of striped muscle. This would seem to me to invalidate the hypothesis advanced by Mr Todd, and to some extent suggested by Mr Porter's work, that idiopathic megarectum may perhaps be due to some defect of the inhibition of the external sphincter ani that normally occurs on continued distension of the rectum – unless of course the puborectalis, which partly surrounds the ano-rectal junction, can be considered to act as a complete



A B

Fig 1 *Barium enema plates in cases of megarectum and megacolon.* A, *Hirschsprung's disease.* B, *Rectal inertia*

substitute for the external sphincter and to display this disturbance of proper relaxation. But I would emphasize that the anus seems patulous in most of the cases with ectopic vaginal anus that have come our way.

Another possible intrinsic abnormality is diminution of the contractile power of the rectal wall. But rectal biopsies have failed to show any quantitative diminution in the ganglion cell population of the rectal wall in these cases, comparable to that found in Chagas' disease, which Professor Santos has described. Also, though Dr Connell's motility studies did reveal a hypomotile condition of the rectal wall in some of his cases of megarectum, in others the pressure recordings were within the limits of normality. Also, as he mentioned, certain people who do not suffer from megarectum have similar hypomotile tracings. It would seem that lack of contractile power in the rectal wall cannot be held to be a consistent cause of megarectum.

Last to be considered as an ætiological factor is the possibility of some blunting of the normal rectal sensation, on account of which the patient allows fæces to accumulate without feeling any urge to defæcate. It seemed to me that there was some discordance between the sensory findings recorded by the opening speakers and our own findings in this matter. We have found that these patients with rectal inertia are quite sensitive to balloon distension of the rectum if a big enough balloon is used, but that, as in Mr Porter's cases, the sensation is experienced not in the sacral region but in the lower abdomen. Also, Mr Nixon claims that rectal sensation is perhaps initially much diminished but returns to normal as rectal distension is reduced by wash-outs, suggesting that there is no inherent sensory defect.

I feel compelled to say that, despite the interesting papers contributed to this Discussion, the precise nature of the essential abnormality present in many cases of idiopathic megarectum or rectal inertia still eludes us.

Surgical treatment of rectal inertia: It has generally been advised that these cases should not be operated on, because to remove the affected part of the rectum entirely would involve a low resection likely to interfere with continence. But there are times when the surgical instinct to excise a large mass rises superior to reason, particularly when faced with patients with a truly enormous megarectum! It is tempting in these cases to remove the dilated bowel in the hope, as Mr Nixon has put it, of giving the patient 'a fresh start in life'. I have twice succumbed to this desire and in neither case was the result encouraging. One young man had a low abdomino-anal resection and unfortunately developed leakage, sepsis and a host of complications for which I had eventually to remove the rectal remnant and give him a permanent colostomy. The other patient, a young boy, had a similar operation with a smooth postoperative course, but he has had indifferent rectal function since and still has to have enemata or wash-outs. I was therefore interested to learn that in Mr Nixon's cases submitted to resection the wash-out regime has also had to be continued. I noted Mr Todd's decidedly gloomy report on the results of different surgical procedures in his cases of megarectum submitted to radical surgery. As a corrective to his depressing record I should like to describe one operation that can be relied upon to give a good result in these cases – though at a price. That is a proximal iliac colostomy, preferably with a divided colon, placing the proximal end in the abdominal wall in the left iliac fossa and the distal end nearer the mid-line in the lower epigastric region. I have now performed this operation on 3 cases, 2 on girls of 8 or 9 years and 1 on a man of 21. Before operation the idea of an artificial anus was naturally repugnant to them and their parents, but now all three patients sing the praises of their colostomies, which seem to them like charms compared with the bother they used to have with their megarectum! I do not suggest that such a colostomy could often be indicated in the management of rectal inertia, but, when medical treatment has apparently failed to keep the patients reasonably comfortable, the surgeon should consider this simple and effective operation as an alternative to any form of resection, which is so frequently followed by continued symptoms and serious complications.

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Sir Denis Browne (*London*)

In the treatment of that variety of 'megacolon' which I consider is better called 'colonic inertia' there is one fundamental principle – that if the rectum is emptied the rest of the colon will look after itself. Purgatives only send more fæces down till the rectum is distended even beyond its already abnormal size; the wash-out with tube and funnel needs skilled administrators and is ineffective on masses of hard fæces; and the ordinary enema may vanish into the dilated bowel with unfortunate results.

What is needed is a method that acts on the rectum and lower colon, that is safe, clean and can be self-administered in privacy by older children or adults. The well-established though little-used technique shown in Fig 1 fulfils all these requirements. An ordinary rubber hot-water bottle is filled with a suitable amount of warm, approximately normal, saline and a tube with shut-off clip is screwed into its neck. The bottle is then

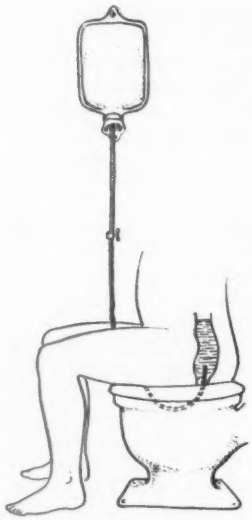


Fig 1

hung up at a height of three feet above the anus when the patient is sitting on a lavatory seat. The fluid is allowed to flow through a plastic tube till mild distension or desire to defæcate is felt, the patient having full control meanwhile by the shut-off clip. Then the tube is withdrawn and the fluid and everything that comes with it is allowed to drop through the relaxed anus: the vertical position of the trunk is a great factor in both safety and efficiency. This routine, taking a very few minutes and attracting no notice to its performance, can be carried out daily till the rectum becomes used to a new state of emptiness.

Small children can be seated on a wooden armchair with a suitable hole cut out, and the necessary control gained by a padded band over the thighs. The tube is inserted from behind, where they can neither see nor grab at it. The whole procedure is usually accepted quite easily, which is by no means the case when the child has to be held down in a horizontal position.

Mr Clive Butler (*London*)
I wish to emphasize the importance of Prostigmin in the treatment of both Hirschsprung's disease and so-called idiopathic megarectum. Since 1937 it has been my custom to have these patients screened in the X-ray department; after an intramuscular injection of Prostigmin it can be clearly seen if the dilated bowel responds or not. In favourable cases patients have been put on a course of oral Prostigmin combined with a suitable purgative; the results in a small number of cases have been encouraging.

[Mr Butler showed two slides illustrating the waves of contraction which occurred in the dilated rectum following intramuscular Prostigmin.]

Mr Ian P Todd, in reply, said that Professor Goligher's remark that a colostomy might give a satisfactory result in these cases bore out his own thesis that there was a disorder of rectal physiology, not colonic. The vaginal ectopic anus was patulous, as the external sphincter ani was not surrounding the orifice. There the puborectalis might not be inhibited normally by rectal distension or the rectum might be atonic and hypo-excitable, or it might be hyposensitive, a frequent finding in these cases. It was, however, frequently inadequate and obstructive.

Mr H H Nixon, also in reply to Professor Goligher, said: (1) He did not recall any case with 'enormous dilatation . . . down to the ano-rectal ring' in which biopsy had revealed Hirschsprung's disease. (2) The value of 'mucosal' biopsy depended on the submucosal and intermuscular plexuses both being absent throughout a Hirschsprung segment. (3) Tables 4 and 5 interpolated in the text gave a longer follow up of rectal inertia treatment. There was objective resolution of the megarectum. (4) The training regime had been used after operative removal of the rectal reservoir, but treatment had not been continued indefinitely.

Mr N H Porter, in reply to Professor Goligher, said that in 12 cases of idiopathic megacolon the position of the anus had been normal. The integrity of the voluntary sphincters had been verified clinically and by electromyography. Investigation of normal and paraplegic patients showed that reflex inhibition of the external sphincter ani and puborectalis was vitally important in normal defæcation. Without inhibition defæcation was difficult and might be incomplete so that fæcal accumulation occurred. Fæcal accumulation might be associated with a high threshold for reflex sphincter inhibition. The extent to which the anal canal would dilate was governed by its size and by pain, so that there was a limit to the dimensions of the fæcal mass which would pass. If the mass needed to establish reflex sphincter inhibition and relax the anal canal was abnormally large it would not pass, no matter how slack the anal canal might become. In this respect, therefore, a high inhibitory threshold would act as an inherent barrier to defæcation. This hypothesis could only be evaluated by further study and a long follow up of cases. Mr Porter questioned the validity of comparing this physiological problem with the host of anomalies, anatomical and functional, which arose in congenital maldevelopments of the pelvic floor.

In the experiments described rectal sensation referred to some kind of desire to defæcate, which was experienced in the perineal or sacral regions and not the abdomen. Finally, he emphasized that sphincter inhibition depended on a reflex arc. The afferent impulses arose from sensory endings in the wall of the rectum. If defects of the inhibitory mechanism existed they might affect any part of this arc. It was not, therefore, possible to exclude sensory defects from investigations at present.

Section of Pathology

President N F Maclagan MD

Meeting February 21 1961

Electron Microscopy

The Electron Microscopy of Normal and Neoplastic Cells

by E H Mercer DSC PHD (*London*)

Biological Application of Electron Microscopy and its Potential

The electron microscope is a relatively new tool in biological research, for it is less than ten years since reliable methods of fixing, embedding and sectioning of tissues for examination in the instrument were developed: a development which has ushered in a new era in cytology.

The techniques for preparing materials for electron microscopy are essentially similar to those of light microscopy. More care must be taken in fixation and, since electrons are readily absorbed by matter, the actual sections must be about 1/50–1/100 of the thickness of those previously used. Otherwise the orthodox histologist will find the technique sufficiently familiar. Certain peculiarities of the instrument concern the biologist: (1) All operations are conducted *in vacuo* to prevent the scattering of the electron beam. This means that (except for very special cases) we cannot study living matter. (2) Since all matter scatters electrons to some extent, the image, which is viewed on a fluorescent screen like that of a television tube, is seen simply in black, white and greys as in an ordinary photograph. Colour does not exist; when an electron microscopist speaks of 'staining' he means a technique for increasing electron scattering to increase the contrast of the image.

The unique advantage of the instrument lies in its magnification and resolving power. Useful magnifications running up to $\times 1{,}000{,}000$ are possible (1,000 times that of the light microscope). A cell 0·1 mm in diameter would be some 100 yards wide at the extreme magnification and it is potentially possible to see everything in it except small mobile molecules such as salts and water.

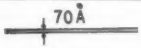
With such a resource we can envisage the discovery of all the structural units of the cell and the stepwise reconstruction of a tissue beginning with its component molecules and building up to complete cells and tissues. With the addition of X-ray diffraction methods, by which individual atoms are located in molecules, we are in a position to attempt a genuine *molecular biology*, i.e. to account for biological phenomena in terms of the molecular structure of the cells and tissues concerned. This has long been the goal of theoretical biology and now, with a continuous microscopic coverage from molecule to organism, we feel it is within our grasp. With the normal functioning of cells understood in terms of molecular structure, their pathological function should prove easier to understand and correct.

The Language of Electron Microscopists

The larger structures of the cell are familiar to all – the nucleus, chromosomes, various cytoplasmic inclusions, mitochondria, &c. A description couched in terms of these objects, their number, size and position in the cell, constitutes cytology at the level of the light microscope. Microscopists try to give an account of larger structures in terms of the smallest they can see. In the case of the light microscopists this means looking for unit structures of the order of 0·2 μ (the smallest objects which can be seen apart must be separated by about this distance which is determined by the wavelength of light used, ~0·3 μ) and describing the larger cell structures in terms of these. Since the smallest of these objects contains hundreds of thousands of molecules, we are far from being able to approach the molecular level by direct observation using light.

Similarly electron microscopists report their findings in terms of objects of a far smaller range of sizes, which their methods reveal as the smallest structural elements common to all cells. The larger objects seen by light microscopists are constructed from these smaller elements and it is part of the problem to lay bare this construction. It is therefore desirable to describe the new objects discovered by electron microscopy and to name them, since these terms are not yet part of the everyday vocabulary of the pathologist.

Table 1
Cellular membrane systems

Name	*Location in figures*	*Appearance in thin sections*		*Chemical nature*
Plasma membrane	Encloses cell (m in Fig 4)	Thin, 70 Å thick double line		Phospholipid plus protein
β-cytomembranes●	Folds connected to plasma membrane and running deep into cell	Resembles plasma membrane and is actually a long invaginated pleat		As plasma membrane
γ-cytomembranes●	Small vesicles throughout cell; stacks of parallel membranes and vesicles in Golgi zone (G in Fig 4)	Thin smooth-surfaced membranes less dense and less thick than plasma membrane		Phospholipid plus protein
α-cytomembranes●	Flattened sacs and stacked paired membranes in basophilic portions of secretory cells (R in Fig 1)	As for γ-cytomembranes but surfaces everywhere covered with dense particles 150–200 Å diameter		Phospholipid plus protein; particles contain RNA and protein
Myelinic forms (membrane whorls, concentric shells, &c)	Irregularly distributed in cytoplasm	As for β-cytomembranes but in form of concentric shells		Same as β-cytomembranes
Fenestrated membranes	Enclosing nucleus = nuclear membrane, or scattered in cytoplasm of some cells (Nuclear membrane in Figs 1–4)	Double membranes covered with a hexagonally arranged system of holes or 'pores'		
Mitochondria	Throughout cytoplasm (M)	Closed, double-walled vessels. Inner wall thrown into folds. Membranes smooth (diameter *c.* 1 μ)		Phospholipid plus enxymes

●For nomenclature, *see* Sjöstrand (1956).

(*a*) *Intracellular membrane systems:* One of the most impressive discoveries of electron microscopy has been the extent and variety of intracellular membrane systems. This feature of cell structure was adumbrated by biochemists who understood the necessity of a 'cytoskeleton' to support the many organized enzyme systems revealed by biochemical methods. The cell membrane, or *plasma membrane*, has long been recognized. Table 1 summarizes the types of membrane at present recognized, with their appearance, location and chemical nature.

(*b*) *Particulate elements of the cytoplasm:* These may be essential cell constituents or specialized products of differentiated cells. They range in size from protein molecules (50 Å diameter and upwards) to large bodies such as secretion granules or fibrils. (1) *Ribosomes.* These dense bodies of macromolecular dimensions (150–200 Å) (Fig 4, P) are found at some time in all kinds of cells. They have been shown by Palade & Siekevitz (1956) to be molecules of protein and *ribonucleic* acid and to be associated with protein synthesis. (2) *Ferritin.* By reason of its high iron content, 23%, the *single* molecules of this protein can often be recognized in cells. It appears to be concerned with iron storage and transfer. (3) *Protein filaments*, usually less than 100 Å in diameter, are found in most cells and accumulate in masses in myoblasts (to form muscles) and in epidermal cells as keratin. (4) The specialized products of secretory cells are usually noted as dense bodies enclosed in a cytoplasmic membrane, e.g. melanin, secretions of pancreas, or thyroid.

The products synthesized in non-secretory cells, e.g. hæmoglobin, collect as amorphous masses between the ribosomes.

(*c*) *Specialized surface organelles:* The structures found at the surfaces of cells are of two kinds (1) those found on *free* surfaces, i.e. surfaces not adhering to other cell surfaces, and (2) those found on confronted (or adhering) surfaces in cellular tissues. (1) *Free surface organelles.* Thin pseudopodes or microvilli (diameter ~0·2 μ) may project from cells (Fig 2). They move in and out and appear rather rigid. Cilia (and flagella) are long microvilli containing a characteristic bundle of nine peripheral pairs of filaments and a single

central pair. They are organs of motility whose whip-like action propels the free cells or moves liquid across fixed surfaces. (2) *Attachment devices on confronted surfaces.* The two plasma membranes of cells which are in adhesive contact appear as dense lines in sections, the two membranes being separated by a thin sheet of material (about 200 Å thick) (intercellular layer) less dense than the membranes themselves. This 'intercellular cement' is believed to contain both proteins and polysaccharides but its exact nature is not known. Its importance is evident, since without it the tissue would fall apart. Further, its adhesive qualities appear to be specific, i.e. like cells stick more strongly to like than to unlike.

In situations where the mechanical strength of a tissue needs to be enhanced, e.g. at the surface of epithelia and between muscle cells, the intercellular space may be increased, denser deposits may be formed between the cell membranes and further dense deposits, sometimes with bundles of filaments sprouting from them, appear in localized areas inside the membranes. These structures are called *desmosomes.*

(*d*) *Secreted extracellular substances:* We are not here particularly concerned with the many extracellular deposits that are to be seen principally between mesodermal cells. The fibrous protein collagen should, however, be mentioned on account of its characteristically banded appearance (periodicity 640 Å), as seen with the electron microscope, which enables it to be easily recognized.

(*e*) *The nucleus:* The nucleus is enclosed by a nuclear membrane composed of two layers both of which are smooth and fenestrated, often with aggregations of ribosome-like particles against the inner face. There are normally no membranous structures within the nuclear cavity itself. The chromosomes appear as dense ill-defined bodies in an amorphous matrix; the nucleoli as dense areas containing particles (ribosomes).

Some Typical Cytological Patterns

A valuable method of classifying cells is in terms of their protein-synthesizing mechanism. We may thus distinguish (1) *growing* and *dividing cells* which synthesize material principally to form new cellular structures, (2) *secretory cells* which produce protein, mucin, &c., for secretion, and (3) *retaining cells* which synthesize proteins that remain within the cell, e.g. myoblasts, erythroblasts, &c.

(*a*) *Secretory cells* (Fig 5A): These cells are usually attached on one surface (proximal) to a basement membrane through which food supplies are passed and have a free surface (apical) whence the secretion leaves the cell. Intracellularly we find the accumulated secretion awaiting expulsion in the apex and at the distal end a remarkable gathering of α-cytomembranes in the form of paired particle-covered membranes (R, Fig 1). Between these may be seen mitochondria (Figs 1–4, M). The Golgi apparatus (stacks and vesicles of smooth γ-cytomembranes) is usually found distal to the nucleus. The nucleus itself is enclosed in a double-layered membrane (γ-type) pierced with small holes (500–700 Å wide). Usually a well-developed granular nucleolus is to be seen.

It is widely believed at the present time that the sequence of events in the synthesis of proteins in this class of cell is as follows (Fig 5A): The long DNA molecules of the chromosomes record in their linear sequence of bases the information that determines the sequence of amino acids in each protein chain (polypeptide). A working copy is made of this sequence in the form of an RNA messenger molecule which leaves the nuclear cavity and joins with a ribosome of the cytoplasm. The ribosomes formed in the nucleus may accumulate as a nucleolus or pass out through the nuclear pores and enter the cytoplasm to become attached to the α-cytoplasmic membranes. Here, in co-operation with the messenger RNA, they act as a template guiding the linear assembly of activated amino acids into polypeptides. The polypeptides pass through the membranes, accumulate in the sacs and drift towards the apex to form secretion granules. The cytology is certainly compatible with this picture.

(*b*) *Protein synthesis in retaining cells* (Fig 5B): A second important class of protein-forming cells are those which retain their protein and do not secrete it. Examples are the erythroblasts which form hæmoglobin and become red blood cells, the myoblasts which form muscle filaments and become contractile muscles, and squamous epithelial cells that form keratin.

These cells (Fig 5B) have a nucleus resembling gland cells but a much simpler cytoplasmic pattern. The α-cytomembrane clusters are absent, the Golgi cluster is poorly developed and the cytoplasm is tightly packed with *free* ribosomes. In such cells we may suppose that synthesis follows a path up to a point identical with that in secretory cells but, since the protein is not to be removed from the cell, it is formed freely in the cytoplasm rather than collected into membranous bags.

(*c*) *Mucin-forming cells:* Mucins are macromolecules composed of a polysaccharide component and a protein. They are formed by a distinct class of secretory cells characterized by an elaborate

development of the smooth membranes of the Golgi zone and a smaller cluster of α-cytomembranes. Although we know little of the biochemistry of these cells, it would seem likely that the protein moiety is formed in the α-cytomembranes and is then transferred to the Golgi system for the polysaccharide to be added.

(*d*) *Cells not engaged in synthesis in the adult state:* Some cells, such as kidney cells, after an embryonic period of structural synthesis, settle down to a specialized function, e.g. water transport, not involving synthesis but requiring an elaborate internal membranous (β-type) apparatus and an abundance of mitochondria which provide the chemical energy necessary for the work performed.

This very brief survey at least outlines the main aspects of several of the principal classes of cells which make up the greater part of the adult body. It is incomplete but will serve as a basis from which to examine tumour cells.

(*e*) *Embryonic cells:* These cells are the precursors of all other cells and must be considered a special case of the *retainer* cell (Fig 5c), since to grow and divide the cells must synthesize and retain the proteins required to form daughter cells. Their cytology has the retainer pattern – an active nucleus, few α-cytomembranes and many free ribosomes. As differentiation develops, the type of synthesis and the cytoplasmic pattern changes: future glandular cells begin to accumulate α-cytomembranes, retainer cells accumulate protein in the cytoplasm, and other cells form more mitochondria and internal smooth membranous systems.

A further feature of embryonic cells is the evidence of *poor intercellular adhesion* shown by the frequent occurrence of wide intercellular gaps between the cell membranes and the absence of desmosomes. In some organs the type of adhesive contact described above develops between cells as they differentiate; in others the cells remain relatively solitary, their surfaces remain convoluted and close contacts do not persist.

The Fine Structure of Tumour Cells

A large number of tumours has been examined by means of the electron microscope and from this work a few definite conclusions may be drawn:

(*a*) All the structural elements of normal cells are found in tumour cells.

(*b*) There is no special structural feature which distinguishes tumour cells (*see below* for virus particles).

(*c*) Tumour cells may be typed according to their protein-synthesizing apparatus, i.e. in terms of the normal patterns outlined above. The cells of a well-differentiated primary tumour resemble closely those of the normal tissue from which they have arisen. In such circumstances we are at a loss to say in what respects the cells are abnormal. The electron microscopist is in fact more at a loss than the histopathologist working at a lower magnification, who has less difficulty in recognizing the large-scale defects in tissue organization which betray the neoplasm.

(*d*) In the more anaplastic tumours signs of cytological disorganization can be detected. The specialized apparatus of secretory cells (massed arrays of α-cytomembranes) is less developed and arranged in a less orderly manner; mitochondria may be more rounded, their internal membrane system less orderly and less like that of normal cells of the same origin; the Golgi membranes persist, but if secretory activity is declining, there may be fewer secretory granules within the membranous sacs (Figs 2, 3 & 4).

(*e*) To the degree that the cells lose their defined differentiation they acquire the pattern of the retainer cell. That is, there is an increase in free cytoplasmic ribosomes accompanying the decline in ribosomes bound to membranes or a reappearance of free cytoplasmic ribosomes in cells whose precursors exhibited a cytoplasm relatively free from RNA and typified rather by the presence of smooth β- or γ-cytomembranes (Figs 2, 4 & 5c). Evidently the cells re-acquire the features that characterize the persistently dividing cell; but all kinds of dividing cell (embryonic, renewal tissue cell *and* tumour cell) share the same characteristics. It is *not* a sign of malignancy, it means simply that the cell is now devoting much of its synthetic machinery towards the formation of protein needed for cell division and the building of further cellular constituents.

(*f*) Associated with the changes described in (*e*) are others which indicate that there is a loss of intercellular adhesion. As mentioned above, the cell membrane has among other functions that of maintaining intercellular adhesion necessary for

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Fig 1 *Section through the centre of a liver cell (rat). Fixation: osmium tetroxide, embedded in Araldite. The cell is in contact with others and the plasma membrane may be seen as a limiting dense line.* N *is the nucleus enclosed in a nuclear membrane; the genetic material appears simply as a fine structureless particulate material.* M *are mitochondria,* R *are the basophilic membranes (α-cytomembranes). Notice the abundance of fine vesicles (γ-cytomembranes)*

Fig 2 *A Walker ascites tumour cell (rat) in isolation. (Higher magnification than Fig 1 and only part of cell can be seen.)* N *is the nucleolus within the nucleus,* M *mitochondria,* R *α-cytomembranes, here poorly developed.* V *are surface microvilli projecting into the extracellular space. Note fine dense particles (ribosomes) throughout cytoplasm.*

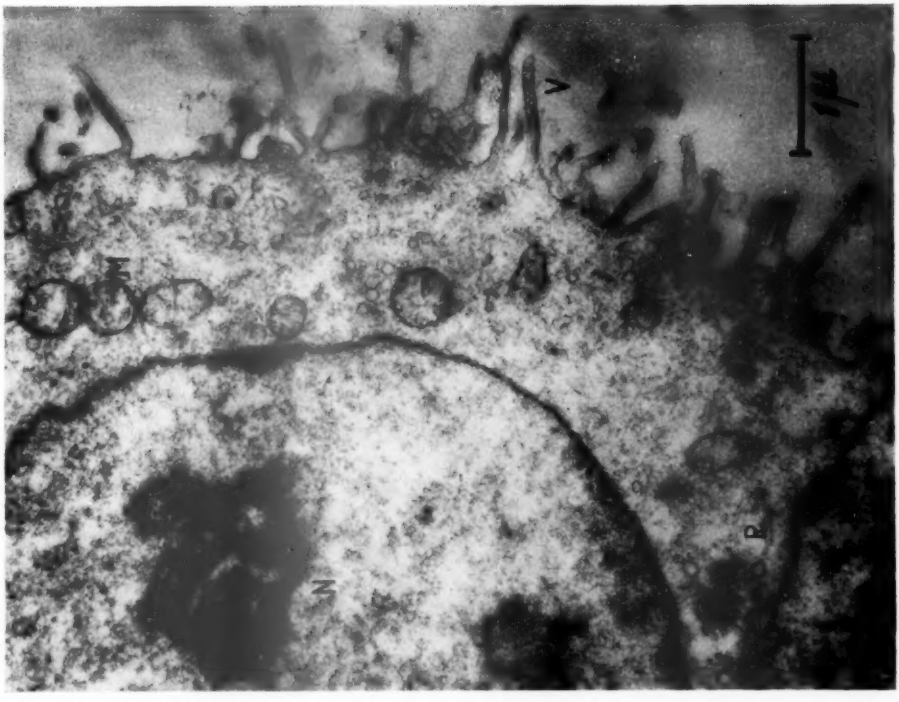

Fig 2

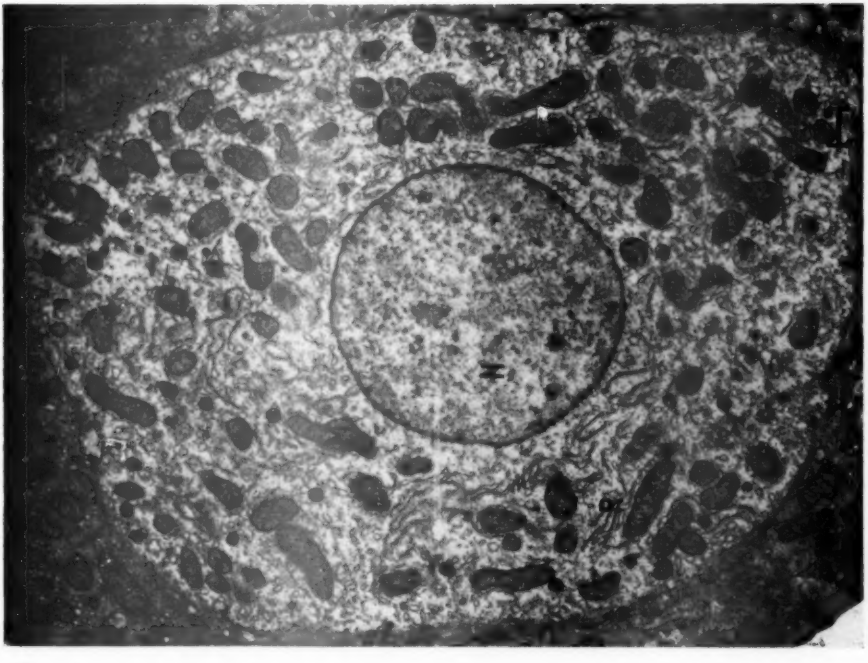

Fig 1
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Fig 3
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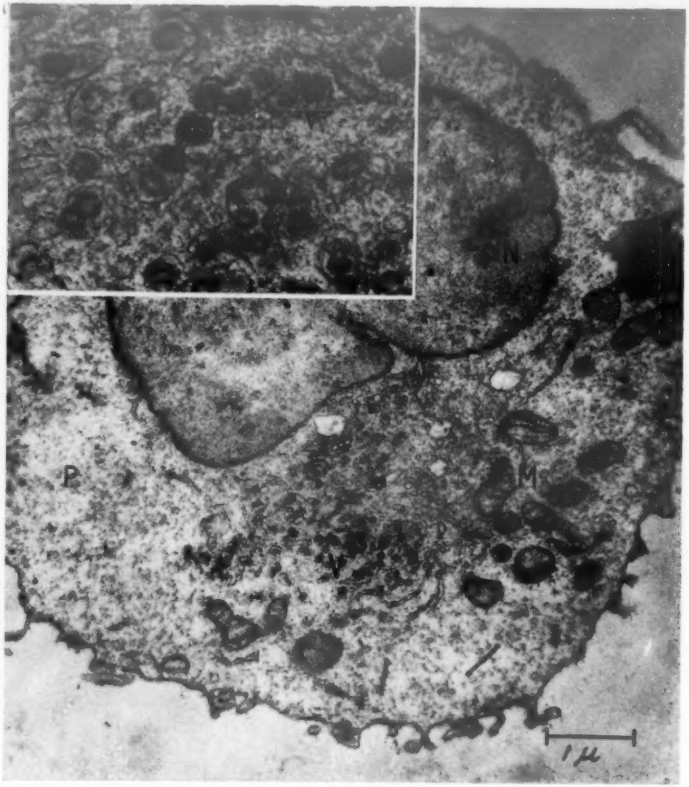

Fig 4

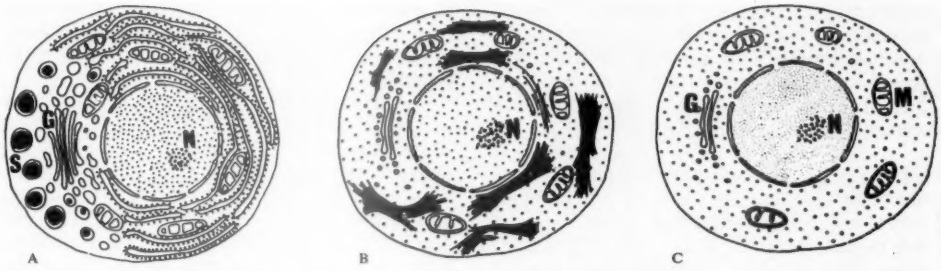

Fig 5 *Cytological patterns of cells engaged in protein synthesis.* A, *Secretory cell: Characterized by massed arrays of particle-covered* α*-cytomembranes.* N, *nucleus containing a well-developed nucleolus.* G, *cluster of smooth parallel membranes (Golgi apparatus).* S, *secretory granules enclosed in membranes.* B, *Retaining cell: Characterized by numerous free particles (ribosomes) in cytoplasm. Bundles of fibrils are shown accumulating in the cytoplasm. Membrane systems are relatively poorly developed.* C, *Generalized cell as typified by an early embryonic cell or a very anaplastic tumour cell (ascites cell).* N, *Nucleus with well-developed nucleolus.* M, *mitochondrion and* G, *Golgi cluster. Note large numbers of free ribosomes and absence of specialized cytoplasmic apparatus*

tissue construction. This is, of course, only in epithelial tissues (or those derived from them) where cells are in direct contact either with each other or with a basement membrane and in such organs as muscles. Many other cells of mesodermal origin are essentially 'free living' and in any case form only transient contacts with other cells.

When cells divide there is evidence to indicate increased surface activity and a partial loss of surface adhesion. This is very obvious in cells maintained in culture, which round-up and 'bubble' when dividing. It is not easy to demonstrate in tissues, but the surfaces of the cells of the dividing germinal layers of many epithelia are usually very convoluted, covered with small villi and separated from their neighbours by wide and variable gaps. Since the surfaces are separated and have configurations suggestive of movement, it is probable that, in tissues also, dividing cells are not adhering so closely and tightly as in the stabilized differentiating layers. A lessening of adhesion may in fact be necessary to permit the movements involved in division.

Many of the cells in malignant tumours give similar electron microscopic evidence of being poorly adhesive. That tumour cells adhere poorly and form weaker tissues was deduced, long before electron microscopic evidence became available, from the ease with which many tumour masses may be dispersed into separate cells. Indeed some have thought it to be a definitive feature of tumours. Our observations show rather that it is a general property of all growing and dividing tissues, which include normal tissues (embryonic and the constantly renewing tissues of the adult – skin, marrow, intestinal mucosa), as well as many tumours. If, after division, the cells proceed to differentiate and take their place in a tissue, the intercellular contacts may appear normal even in a tumour. Thus in many primary tumours (in confirmation of observations made using the light microscope) one may find what appear to be perfectly normally differentiated areas with stabilized cell contacts.

This conclusion does not alter the fact that many tumours (particularly on transplantation in animals) become progressively more anaplastic and this condition is characterized not only by the loss of the internal apparatus of differentiation described above, but also by a progressive deterioration of intercellular adhesion. Such cells spend less time than usual in a non-dividing condition (i.e. they have a lessened tendency to differentiate) and their surfaces thus remain in a mobile non-adhesive condition. The inability to produce the materials required to stick the cells together may be regarded as an addition to the list of losses suffered by such cells which we group

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Fig 3 *From a myosarcoma (human) showing a nucleus with two nucleoli,* N*; many mitochondria* M *of the type found in striated muscle; traces of myofilaments may be seen at* F*;* S *is a sarcolemma type of membrane bounding each cell and identical with that noted in muscle;* C *indicates short sections of collagen fibrils, part of the sarcolemma. The tumour was scarcely recognizable as being of muscular origin but has the several typical features noted. (Original specimen from Dr I Hamlin, Royal Marsden Hospital)*

Fig 4 *Cell of a mouse lymphoma (5 days old) and eight hours after treatment with a cytotoxic agent.* m, *plasma membrane;* N, *nucleus;* F, *fat droplet;* G, *Golgi zone;* M, *mitochondria;* P, *ribosomes. In the vesicles of the Golgi zone may be seen virus-like particles,* V, *shown enlarged in the inset in the top left hand corner. (Original specimen from Dr K Lapis, Chester Beatty Research Institute)*

For legends see opposite

together by calling them anaplastic. Ultimately the cells may lose almost all evidence of adhesiveness and we reach the condition of the literally 'free-living' cells found in the ascitic fluid (Figs 2 & 4). These divide without resting and have scarcely any tissue-forming tendency.

(*g*) *Virus-like inclusions:* Not uncommonly virus-like objects are found in the cytoplasm of tumour cells (Fig 4, V). In some instances we are certain that these particles are the carcinogenic agent; in others their effect on the cell is not clear. The possibility exists that they may have simply entered the cell in the course of the normal feeding in which the cell may engulf extracellular particles. A fuller account of the relationship between viruses and tumours will be found in the article by Oberling & Bernhard (1961).

Acknowledgments

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Mr Michael Docherty very kindly made the photographic enlargements.

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Electron Microscopy of Human Biopsy Material

by I Friedmann MD (*London*)

In his work, the pathologist-light-microscopist is guided mainly by personal experience. The pathologist-electron-microscopist, for the present at any rate, may have to rely more on the experience of the anatomist, embryologist and others, who have been quicker off the mark in applying the electron microscope to the study of healthy tissues. There has indeed been a renaissance of the study of normal histology during the past decade; it is, moreover, not difficult to recognize that electron microscopy as applied to the study of diseased tissues has been gathering momentum, and is going greatly to widen the horizon of general pathology.

The fine structure of tumour cells has been widely studied by several workers (Bernhard 1958). Nevertheless, Bernhard's suggestion remains valid: 'that further systematic investigations of all neoplasms, experimental and human, and irrespective of their site or origin, are desirable.' It may be added that systematic electron microscope investigations ought to be applied to the study of non-neoplastic diseases.

This, in fact, has been the object of the present investigations and the fine structure of non-neoplastic and neoplastic conditions affecting the ear, nose and throat has been studied. Although the material so far collected awaits complete investigation, some of the main observations may be outlined here to illustrate the uses of electron microscopy in pathology.

General observations: The essential technical skill and microscopical experience can best be acquired on experimental material such as animal tissue or tissue cultures, which, as regards fixation and embedding, offer more readily adjustable conditions. Tissue cultures of the isolated fowl embryo otocyst served these purposes in our laboratory before we embarked on human biopsy material (Friedmann 1959, Friedmann & Bird 1961).

Human biopsy material is more treacherous owing to the considerable sampling error. Occasionally, the presumptive clinical diagnosis may prove inaccurate. Furthermore, degenerative and necrotic changes in the diseased tissue may jeopardize the quality of the picture and so the final result.

Material and methods: Tissue from 90 biopsies fixed in Veronal-buffered 1% osmic acid containing 3% dextran and 0·25% sucrose were embedded in methacrylate and Vestopal W, sectioned on a Huxley-type ultramicrotome and examined under a Siemens Elmiskop I. Blocks of the tissues embedded in Vestopal W were stained *in toto* with 0·5% phosphotungstic acid in alcohol, and thin sections were frequently stained with 2% uranyl acetate. Sixty-two biopsies proved suitable for electron microscopy.

Observations on human biopsy material: The observations will be described under three main headings: (1) General morphology of the examined tissues in low-power electron micrographs. (2) Fine structure of the relevant or representative cells: eosinophils; plasmacytes; neoplastic cells. (3) Unusual nuclear or cytoplasmic observations: nuclear and crystalline inclusions.

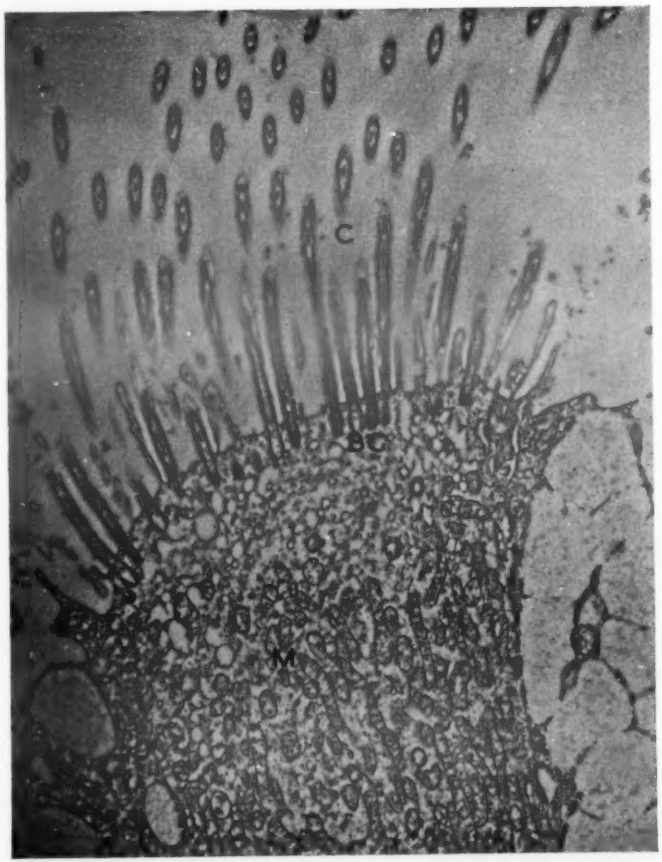

Fig 1 *Hair cell in nasal mucosa of allergic type nasal polyp flanked by secretory cells. Note cilia* (C) *on cellular surface growing from basal corpuscles* (BC). *Cytoplasm contains densely packed mitochondria* (M). ×*10,000*

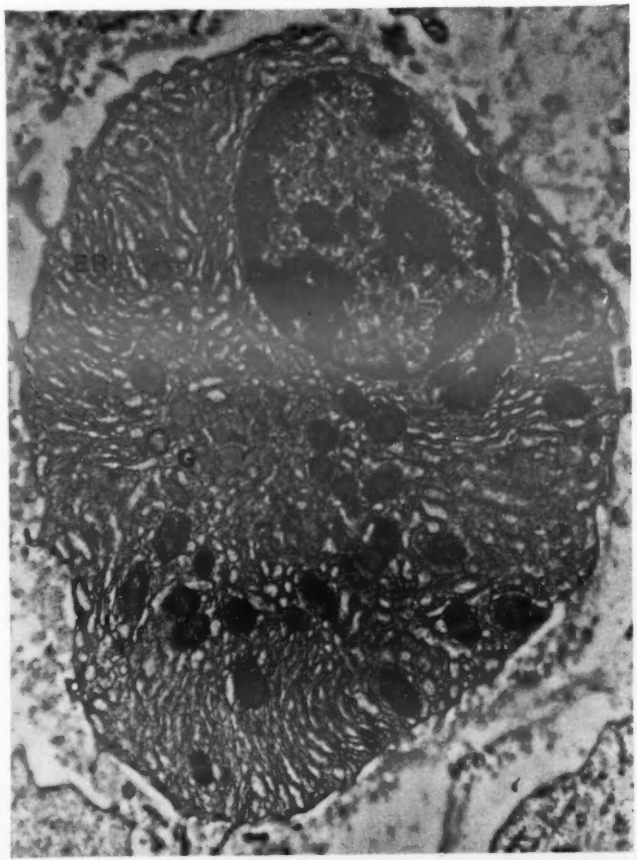

Fig 2 *Plasmacyte in nasal polyp displaying characteristic rich ergastoplasm. The eccentric nucleus* (N) *shows 'cartwheel' arrangement of chromatin. There are numerous mitochondria* (M) *and homogeneous granules present between the cysternæ* (ER) *and in the Golgi body* (G). *Vestopal.* ×*7,900*

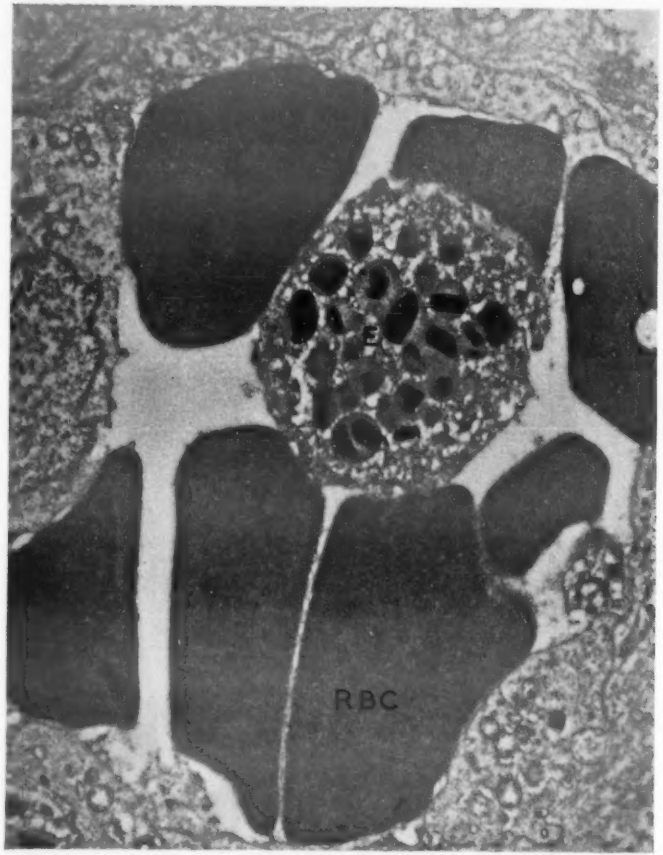

Fig 3 *Allergic type nasal polyp. Small capillary containing red blood corpuscles* (RBC) *and an eosinophil* (E). ×*9,400*

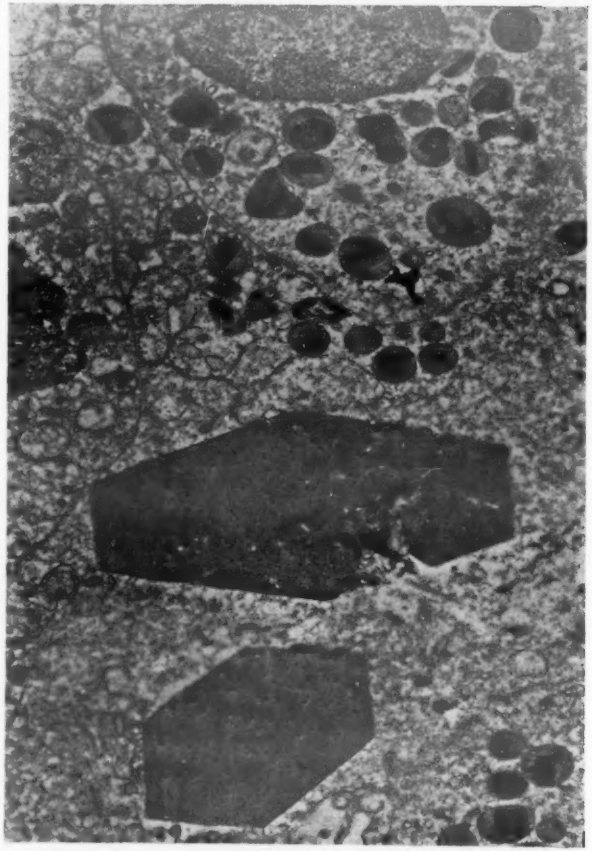

Fig 4 *Allergic type nasal polyp. Note two hexagonal crystals in cell between two eosinophils.* ×*9,450*

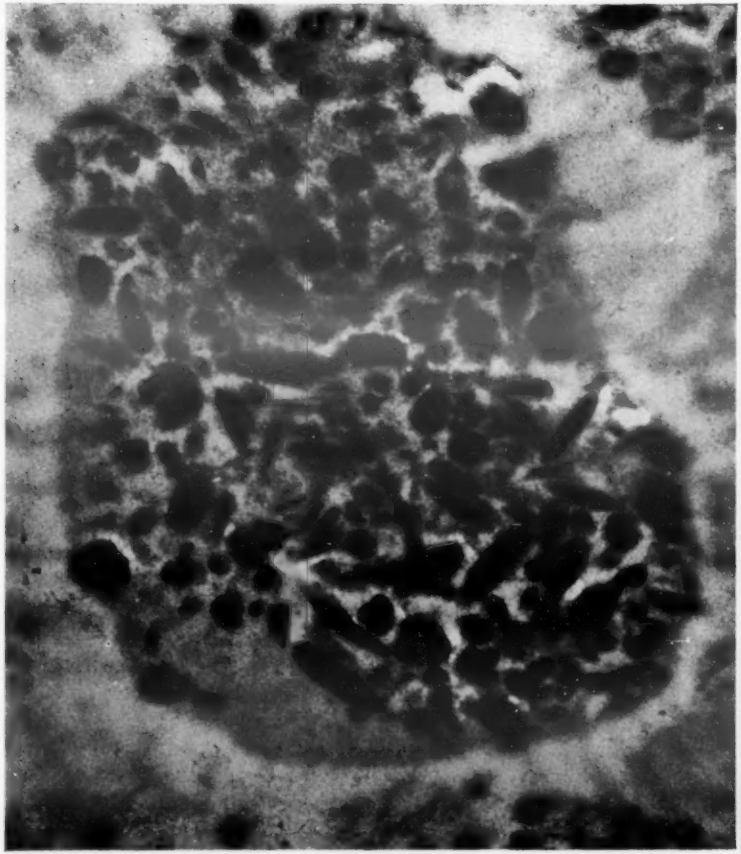

Fig 5 *Melanin granule in malignant melanoma of nose consisting of vast numbers of small melanin particles. Formol fixed.* ×*31,250*

Fig 6 *Detailed picture of desmosomes or attachment zones of well-differentiated squamous cell carcinoma of vocal cord. Normal structure of attachment plaques* (AP) *into which tonofilaments* (T) *insert. Note granular material filling intercellular space* (IS). ×*53,300*

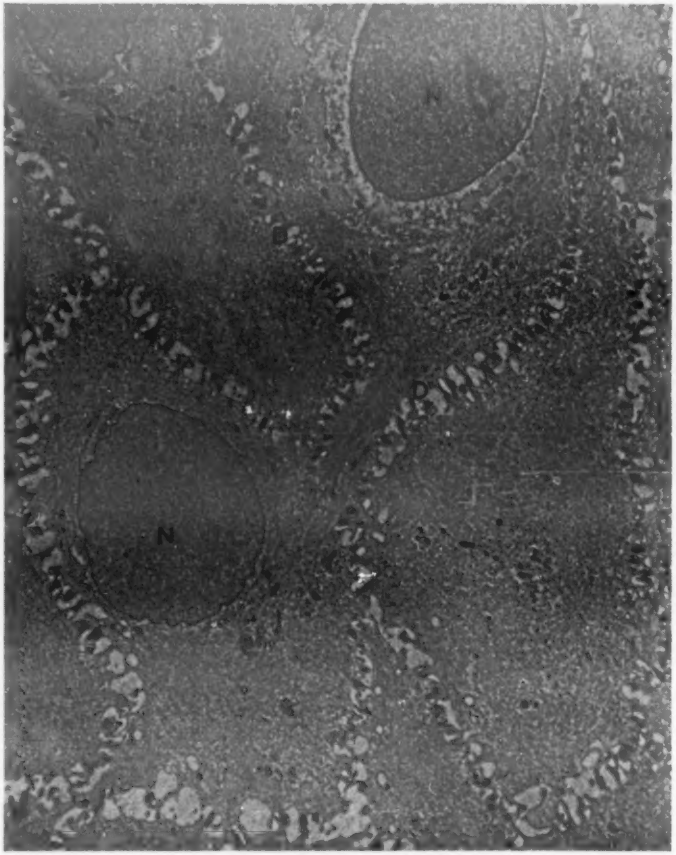

Fig 7 *Squamous epithelial cells of juvenile papilloma of larynx. Note large numbers of more or less closely spaced desmosomes* (D) *or intercellular bridges. No virus particles seen at higher resolutions.* ×*3,700*

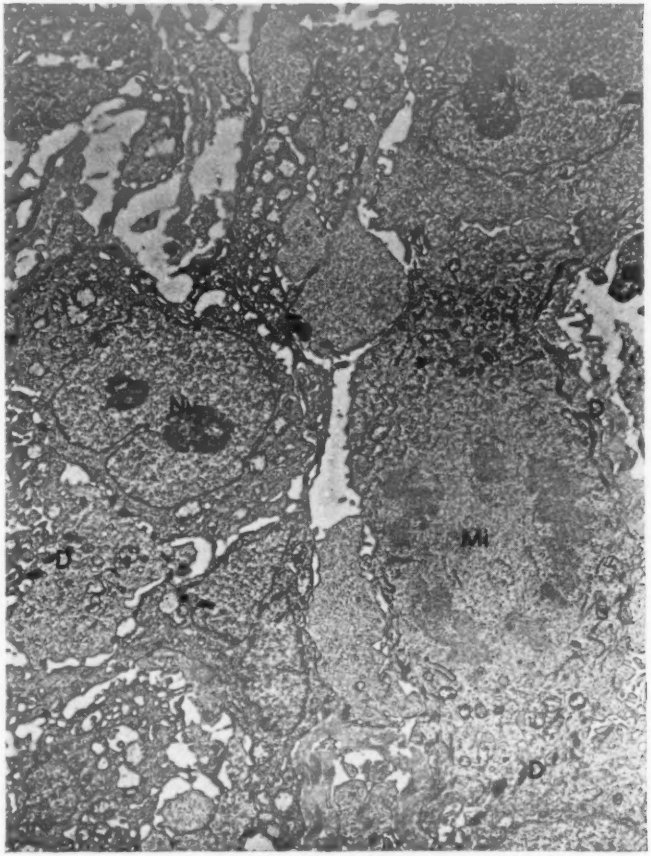

Fig 8 *Squamous cell carcinoma of the larynx. Note mitotic figure* (Mi), *distended intercellular spaces and comparatively small number of desmosomes* (D). *Also large nuclei with prominent nucleoli* (Nu). ×*4,000*

Biopsies from the Nose (12 Cases)

General morphology: The surface epithelium of the nose and sinuses is composed of ciliated hair cells flanked by secretory cells (Fig 1). The hair cells possess large numbers of cilia arising from basal corpuscles embedded in the cells. The secretory cells contain large secretory granules or vacuoles. The columnar epithelium may be more or less intact or show degenerating and atrophic changes leading to destruction of the ciliated surface and causing variations in the shape and size of the goblet cells. It may be replaced by metaplastic squamous epithelium showing the characteristic fine structure of squamous epithelium described below (p 1070). There are polygonal cells in the intermediate layers and the basal layer consists of cuboidal cells resting on the basement membrane. The basal cells are easily separated by œdematous fluid and reveal large numbers of microvilli but only a few or no attachment zones.

The undulating basement membrane consists of a double membrane separated by a greyish zone, *lamina densa*, about 600 Å wide. The 'hyalinized' band observed under the light microscope in allergic type polyps appears as a more granular zone containing collagenous fibres which blends imperceptibly with the œdematous stroma. Here, one encounters varying numbers of inflammatory cells, two of which merit particular attention: the eosinophil and the plasmacyte.

Fine structure of the eosinophil: The eosinophil can readily be identified by its granules containing characteristic dense inclusions of various shape and size, with bar-shaped or polygonal inclusions predominating (Fig 3). The variation in shape and size may be entirely due to the plane of sectioning of a basically plate or disc-shaped inclusion. On the other hand, some variation in the basic shape of the inclusions cannot be excluded. The number of granules varies from 10 to 30 or more in a cell. The nucleus of the eosinophil is often lobulated but may be spherical.

Fine structure of plasmacytes: The plasmacyte displays, as under the light microscope, a characteristic fine structure (Fig 2). There are in the cytoplasm densely arranged granular cysternæ of the ergastoplasm; the cysternæ appear more densely packed in osmium-fixed tissues, but distended and separated from each other in cells fixed in formol saline. The distended cysternæ often contain greyish homogeneous granules of protein nature and there are numerous scattered mitochondria present. The eccentric nucleus displays clearly the characteristic cart-wheel pattern. In the infranuclear zone there are no cysternæ and mitochondria are scarce. This area corresponds with Marschalko's space and contains the Golgi body,

Charcot-Leyden crystals: Hexagonal or elongated wedge-shaped or pyramidal crystals were observed in fairly large numbers in several polyps containing large numbers of eosinophils (Fig 4). There were also irregular or blunt cigar-shaped structures present, usually surrounded by densely packed eosinophilic granules. The eosinophilic granules themselves appeared to be well preserved and the homogeneous crystals showed no inclusion resembling eosinophilic granules and no crystalline pattern.

Welsh (1959) first studied the development of Charcot-Leyden crystals in eosinophils in thin sections under the electron microscope. White (1954) observed Russell bodies and crystalloid inclusions in the plasmacytes of the spleen of sensitized rabbits and mice. Crystalloid inclusions were described by Wellensiek (1957) in thin sections of plasmacytes in the mesenteric lymph nodes of healthy rats.

We found large globular droplets in nasal polyps resembling Russell bodies as seen under the light microscope. Some were too small and could only be seen under the electron microscope. As the plasmacytes often contain greyish secretory protein granules it may be suggested that abnormal cellular metabolism could lead to the formation of Russell bodies followed in some cases by crystallization of the cellular proteins.

The present observations together with those of other workers suggest that the crystals may be formed in at least three ways: from eosinophilic granules as suggested by Welsh (1959), from plasmacytes, or caused by virus action. This question is being studied.

Nasal Neoplasms (9 Cases)

The examined material included several cases of squamous cell carcinoma, the fine structure of which resembles that of similar tumours of the larynx to be described later in this paper.

Others included *fibrosarcoma of the ethmoid* consisting of elongated needle-shaped cells forming a monotonous, almost syncytial pattern.

A case of *plasmacytoma* proved more instructive. Although, or because, the tissues were fixed in formol saline, the ergastoplasmic pattern of the plasmacytes was clearly visible. This case illustrates some of the practical help electron microscopy may occasionally provide. The light-microscopical appearances of this neoplasm were difficult to interpret and the diagnosis lay between plasmacytoma and reticulum cell sarcoma. The information provided by the electron microscope assisted in arriving at the diagnosis of plasmacytoma.

Malignant melanoma of the nose: Although all four specimens were received in formol saline, the pattern of pigmentation could readily be studied. The cytoplasm of the melanotic cells contained granules which, at high magnification, consisted of large numbers of smaller irregularly shaped sub-units of pigment revealing at much higher resolutions further smaller sub-units. The electron dense 'black' pigment granules stand out clearly against the grey protein matrix (Fig 5).

Biopsies from the Larynx and Pharynx (29 Cases)
General morphology: In low-power electron micrographs of squamous cell papilloma or carcinoma of the larynx or pharynx the general features appear much the same as in light microscope preparations. At higher magnifications adjacent cytoplasmic membranes of two squamous cells of the stratum spinosum show, at intervals in the membrane, localized areas of increased density into which short or long bundles of tonofilaments insert. This complex structure, the *desmosome*, has been generally accepted as the electron microscopic counterpart of the intercellular bridge as seen under the light microscope. Desmosomes are distributed at random and in large numbers around the cells of the prickle cell layer. The function of the desmosome is mainly the mechanical one of assuring the adhesion of the epithelium.

The fine structure of the normal desmosome: The normal desmosome as seen in healthy squamous epithelium of the larynx and in juvenile recurrent papillomas (Fig 7) consists, as in the epidermis, of two apposed plaques which are specialized areas of the cytoplasmic membrane of the cells involved, separated by a series of alternate dark and light lines as described by Odland (1958). The tufts of tonofilaments are inserted into the plaques and do not, as a rule, traverse the intercellular space between the plaques. The spaces often contain granular material, the nature or importance of which is as yet unknown (Fig 6). The desmosome reacts with PAS and this reaction persists after hydrolysis with saliva and diastase. It is faintly sudanophilic. Hibbs & Clark (1959) suggested that some part of the complex structure of the desmosome is a polysaccharide, possibly associated with a lipid or lipoprotein.

Desmosomes in squamous cell carcinoma: Differentiated squamous carcinoma cells are almost indistinguishable from normal squames and usually carry the normal complement of well-formed desmosomes (Fig 6). Cells of the invasive layers, however, are poorer in desmosomes which vary considerably in size and shape. This may be interpreted as the ultrastructural substrate and one of the causes of the *reduced adhesiveness* of the malignant cell (Coman 1944). These cells usually possess large numbers of microvilli (Fig 8). The cells of anaplastic carcinomas, as expected, show only small numbers of desmosomes irregularly distributed over the surface of the tumour cell which is richly endowed with microvilli consistent with the increased cellular activity.

Nuclei and nucleoli: The nuclei of carcinoma cells are large and the nucleo-cytoplasmic ratio greatly reduced. The enlarged nucleoli may be multiple and show a patchy, coarse pattern. The nuclear membrane is irregular and crenated. There are deep invaginations and indentations which, dependent on the plane of sectioning, may appear as peculiar nuclear inclusions as also observed by Ashworth *et al.* (1960) in certain human malignant neoplasms. The inclusions are formed by cytoplasmic material and surrounded by a 'membrane' provided by the nucleus.

Mitoses are less frequently encountered owing to the comparatively small number of cells seen in a given section and the low contrast of chromatin in thin sections. Mitotic nuclei were occasionally observed, e.g. in a squamous cell carcinoma of the larynx and of the ear.

Mitochondria: There were frequently large numbers of well-formed mitochondria present. Degenerate mitochondria were uncommon in well-preserved carcinomatous tissue but occurred in necrotic parts of the growth.

Biopsies from the Ear (12 Cases)
General morphology: The general morphology of the human ear has not yet been studied by electron microscopists for various reasons. The fine structure of the animal ear, however, has been extensively studied (Wersall 1956, Friedmann 1959, Iurato 1960). Most of the pathological specimens presented no features peculiar to the ear which might distinguish them from similar lesions elsewhere.

Plasmacytic aural polyps consist of plasmacytes possessing a characteristically rich ergastoplasm and eccentric nuclei.

A case of *eosinophilic granuloma* showed typical eosinophils and histiocytic elements of various size and shape.

Squamous cell carcinoma: The well-differentiated cells showed a high degree of keratinization. There were occasional mitoses, otherwise their fine structure appeared to be similar to that of the laryngeal carcinomas.

A tumour more or less specific to this region is the *tumour of the glomus jugulare*. Boyd *et al.* (1959) gave the first description of the fine structure of a tumour of the glomus jugulare processed in this department. In addition, through the co-operation of Mr A Griffith, to whom we are indebted for this valuable material, two additional specimens were embedded for thin sectioning. This vascular tumour consists of epithelioid glomus cells and pericytes with long granular processes. A small number of nerve axons is usually present in the tissue.

Protein crystals in a tumour of the glomus jugulare: There were in one of the tumours, fairly large, round granular inclusions lying deeply in the cytoplasm of the epithelioid cells usually near a nucleus but not closely linked with it. The granules contained tiny crystals consisting of a lattice of small particles arranged in rafts. Miller (1960) described some granular inclusions in the collecting tubules of mice injected with hæmoglobin. As tumours of the glomus jugulare are very vascular, and hæmorrhage is common, breakdown products of blood may provide the raw material of these and similar inclusions.

In summary, there can be no doubt that the electron microscope has an important role to play in the study of human disease. It may not, as yet, serve as a routine diagnostic tool, but it is a method that in a given patient or in the study of a disease, might supply the important and perhaps vital clue. Moreover 'routine' electron microscopy assists in a better understanding not only of the fine structure of diseased cells, but adds a new dimension to light microscopy.

Acknowledgments: This study was aided in part by a grant from the British Empire Cancer Campaign, which is gratefully acknowledged. I am indebted to the Surgical and Theatre Staff of the Royal National Throat, Nose and Ear Hospital for their helpful co-operation. My special thanks are due to Mr E S Bird for technical and research assistance and to Mr R Nunn for assistance with light photographic work.

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The Electron Microscopy of Viruses

by M A Epstein MA MD PhD (*London*)

That the electron microscope can make visible a wealth of hitherto hidden structures is so widely known to-day as to need no emphasizing. Nevertheless, this represents an immense advance, and the use of the instrument for descriptive morphology is clearly essential to build up a basic corpus of knowledge relating to fine structure in all possible fields of study. But in addition to this, there are other less immediately obvious uses of the electron microscope which call for comment and it is the purpose of this communication to describe some of these in connexion with viruses.

Particle Counting

An important aspect of the investigation of the basic biological nature of viral agents concerns the study of their structure and composition. But before a virus can be investigated in this way it must be identified, and it is here that the electron microscope can play an important part if it is used in close conjunction with conventional biological tests for infectivity. For example, in the case of a fairly pure preparation of virus particles in suspension, the number of infective doses present in a given unit volume can readily be determined biologically; but this gives no information about the number of individual virus particles needed to form an infective dose, often a point of great significance in the investigation of virus behaviour.

It is here that the electron microscope comes in, for by mixing the virus suspension with a suspension containing a known number of artificial particles, such as latex, and examining a minute drop of the mixture at an appropriate magnification, the number of virus particles can be compared to the number of latex particles and thus counted and related to the infective dose (Williams & Backus 1949). The way this has been done in the case of the adenovirus (Pereira & Valentine 1958) is shown in Fig 1; the preparation has been mounted whole and lightly coated with metal to give it a three-dimensional appearance thus allowing the latex spheres to be clearly distinguished from the smaller virus particles.

Checking of Purity

Apart from particle counting, the electron microscope has other important uses in combined biological and morphological work. First, it can be of unique value in determining the purity of a virus preparation; if a suspension of virus is subjected to a sufficient centrifugal force, all the formed structures it contains will be deposited in a pellet, and if samples of the pellet are then ex-

amined in thin sections with the electron microscope, the components present can be recognized by direct observation and their homogeneity assessed (Epstein 1958*a*). An electron micrograph of a part of a pellet prepared in this way from a purified suspension of adenovirus (Epstein & Powell 1960) is shown in Fig 2 and it can be seen that it is composed entirely of uniform particles measuring about 60 mμ in diameter.

Identification of Virus

If the type of experiment just described is extended to include tests for biological activity at each stage, the electron microscope can play a further role by helping to establish the viral nature of particles such as those shown in Fig 2. This has been done with the adenovirus (Epstein & Powell 1960) and the results have shown that about 99·9% of biological activity of the virus suspensions was eliminated during the centrifugation and came to lie in that part of each pellet shown by electron microscopy (Fig 2) to be occupied solely by uniform particles of the appropriate size and shape. Identical results have been obtained in similar experiments with vaccinia virus (Epstein 1958*a*) and the Rous virus (Epstein 1958*b*); in each case the particles could be identified as virus by virtue of the infectivity with which they were associated. Fig 3 shows an electron micrograph of a thin section cut through the appropriate zone of a vaccinia pellet and Fig 4 shows one from a Rous pellet.

Study of Structure

Once the nature of any given particle has been determined, the details of its fine structure can be investigated.

Surface configuration: Until a few years ago the best that could be done was to place a suspension of virus on a specimen support, dry off the suspending fluid, and lightly coat the preparation with metal to bring it into relief (Williams & Wyckoff 1944, 1946). In this way information was obtained about the overall shape and size of different viruses, some of which, like the bacteriophage shown in Fig 5, proved quite striking in appearance. But the procedure only touched the surface of things rather crudely and, with advances in thin sectioning techniques (reviewed by Farquhar 1956) and their perfection, more profitable methods of investigation became available. Quite recently, however, Brenner & Horne (1959) have introduced a new procedure for examining the surface of minute objects, which is capable of revealing remarkable surface detail. Applying this to the adenovirus (Horne *et al.* 1959) the subunits which form the outer coat or viroplasm of the agent have been defined; the ordered pattern in which they are arranged is clearly visible and has enabled an accurate model of the exterior to be constructed (Fig 6).

Internal organization: Where studies of virus structure are concerned with the inner organization of virus particles, thin sectioning techniques which allow the interior of an object to be visualized are of great value and have been employed in several laboratories.

Using the adenovirus as an example once again, particles from the virus-containing zones of pellets have been examined at high magnification (Epstein 1959) following fixation with permanganate (Luft 1956). This fixative has certain specific merits and gives excellent preservation of viruses throughout the material to which it is applied. The adenovirus (Fig 7) measures about 60 mμ in diameter, has a central electron dense nucleoid and a hexagonal profile which is well maintained after embedding and sectioning. In the very thinnest sections the nucleoid can be seen to contain two structurally differentiated elements, an amorphous diffuse material and a thread-like component which, in particles favourably orientated to the plane of section (Fig 7), can be seen to be arranged in curving parallel array.

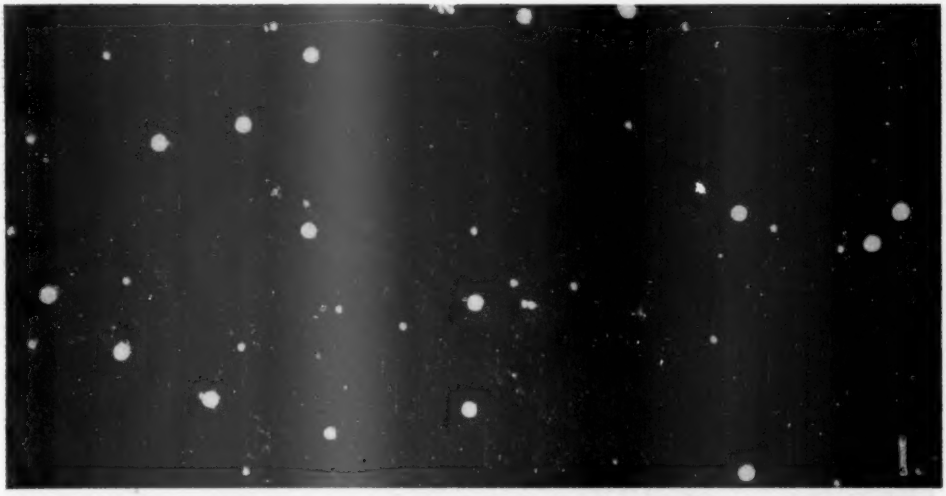
Other viruses examined in the same way have likewise been found to have their own characteristic morphological features. The relatively large vaccinia virus (Fig 8) is shaped like a short, slightly flattened brick with rounded edges and ends and measures about 200 × 300 mμ. It consists of an outer double limiting membrane covering a narrow zone of low electron density, except at the centre of each of the widest surfaces of the particle where a dense lateral body is interposed. Within this outer part a further double membrane limits the central nucleoid which is in turn differentiated into a dense disc-shaped area with a less dense region around it (Fig 8).

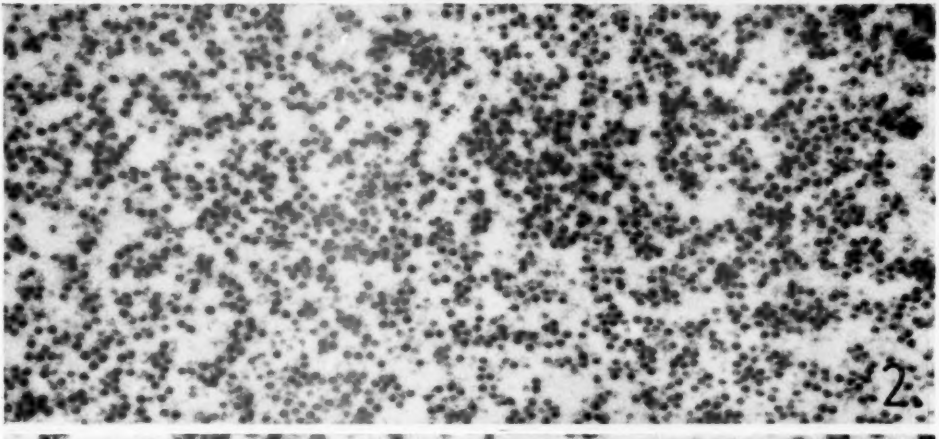
All the figures are electron micrographs; apart from Figs 1, 5 and 6, they are of thin sections of permanganate-fixed virus particles

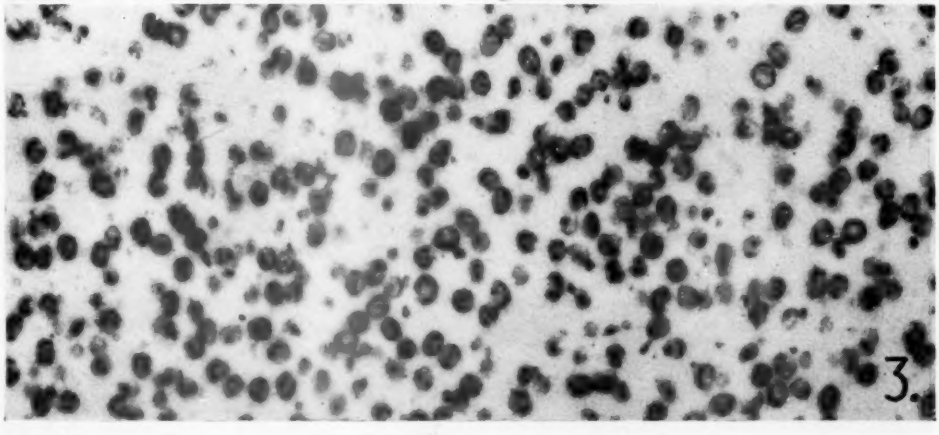
Fig 1 *Typical droplet used in making virus particle counts. The larger spheres are latex indicator particles (0·16 μ diameter) and the smaller dense objects the adenovirus particles. The droplet has been metal-shadowed with palladium. (Reproduced from Pereira & Valentine, 1958, by kind permission)*

Fig 2 *Survey picture of a typical area in the virus-containing portion of an adenovirus pellet. Uniform virus particles about 60 mμ in diameter are the only formed structures present. × 20,000. (Reproduced from Epstein & Powell, 1960, by kind permission)*

Fig 3 *Survey picture of the virus-containing zone of a vaccinia pellet. The randomly orientated uniform particles measure about 300 × 200 mμ. × 13,000. (Reproduced from Epstein, 1958a, by kind permission)*







Figs 1, 2 & 3
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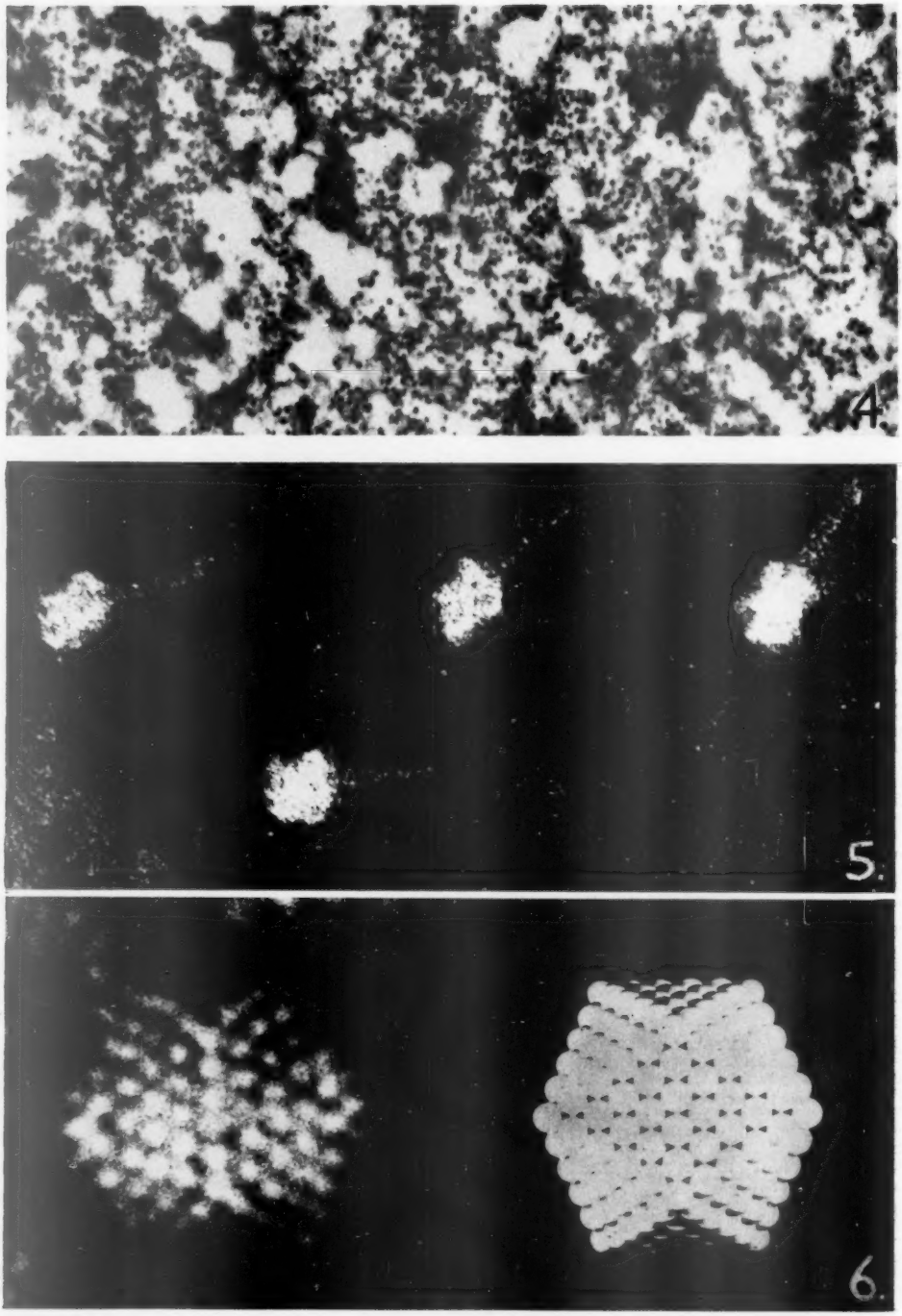

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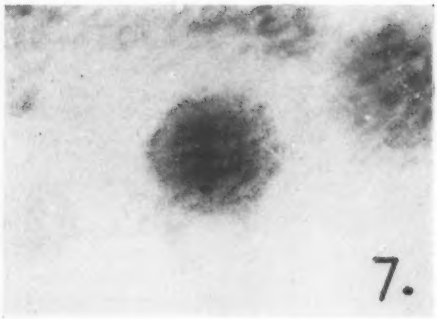

Fig 7 *Very thin section through an individual adenovirus particle showing the hexagonal profile and the structure of the nucleoid with its diffuse material and thread-like component arranged here in parallel curving array. ×300,000. (Reproduced from Epstein, 1959, by kind permission)*

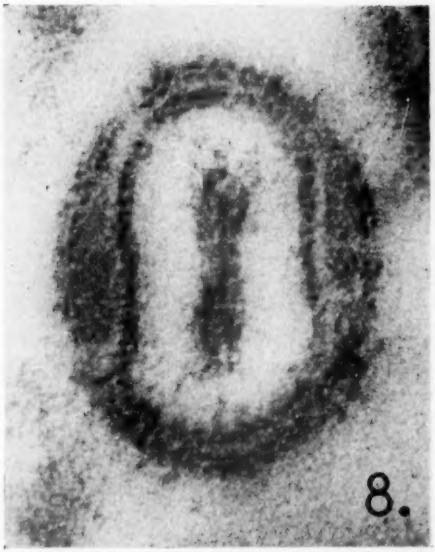

Fig 8 *Longitudinal section across the shortest dimension of a vaccinia virus particle. The double outer limiting membrane covers a narrow zone of low electron density except at the centre of each of the two widest surfaces where a dense lateral body is interposed. The narrow low density zone is limited centrally by a further double membrane surrounding the inner body or nucleoid, which is itself differentiated into two regions. ×200,000. (Reproduced from Epstein, 1958a, by kind permission)*

The Rous virus (Fig 9) also has a central dense nucleoid, but is spherical and measures only 70 mμ in diameter. It too has a double outer limiting membrane and there is a fine membrane between the viroplasm and the nucleoid which can best be seen in particles subjected to appropriate incubation procedures (Fig 10).

Virus Composition

Features of fine structure such as those just described are valid so far as they go and illustrate what can be done with the electron microscope in its obvious role as a tool for descriptive morphology. But morphological information provides no more than a starting point, since it explains nothing about the far more important question of structure in terms of composition and thence, another step away, in terms of function.

Virus composition can be reliably determined by chemical analysis, but for this complete purification is a prerequisite, and one which is often extremely difficult both to attain and to assess (Burnett 1955). Furthermore, although analysis can show of what a virus consists as a whole, it cannot give information regarding the nature of the various morphological structures within each virus particle. As has been pointed out elsewhere (Epstein 1960), such knowledge can only be attained by examining these structures *in situ* and combined electron microscopical and cytochemical methods for doing this have recently been introduced (Epstein & Holt 1958, Epstein *et al.* 1960). The procedure consists of applying specific enzymic digestions to viruses and observing in sectioned material with the electron microscope, the resulting changes caused within different parts of the particle, just as is done with cells and the light microscope in conventional cytochemistry. In addition, the validity of the results can be confirmed by specific cytochemical staining of material whose submicroscopic nature has been checked by electron microscopy.

Continuing to use the adenovirus as an example, in experiments of the kind just outlined, virus-containing samples of adeno pellets were fixed as before with permanganate, which, unlike the more usual fixatives for electron micrsocopy (Palade 1952, Caulfield 1957), has been found to have the valuable advantage of permitting subsequent digestion of appropriate substances by

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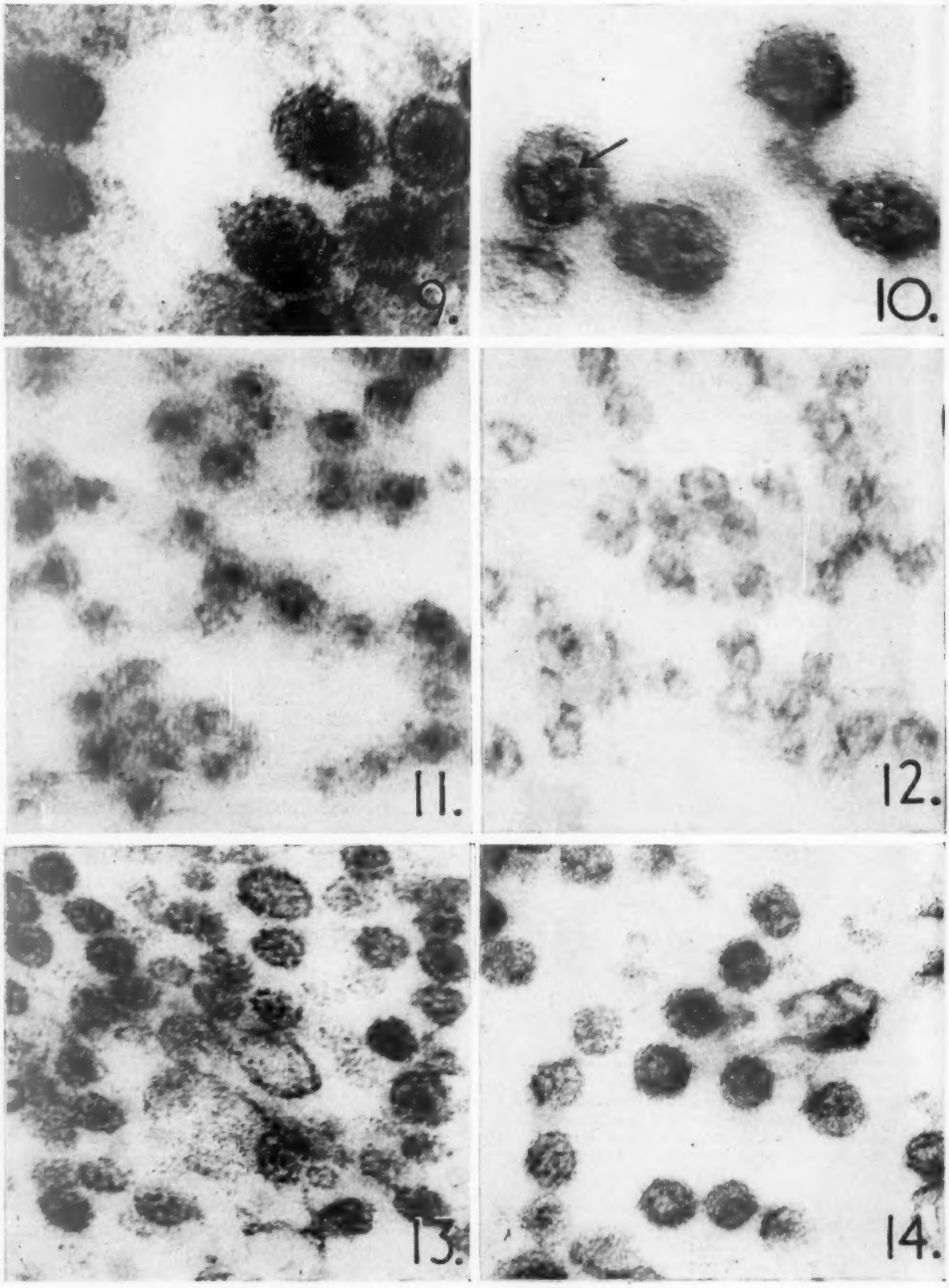
Fig 4 *Representative area of the virus-containing zone of a Rous pellet. The particles are about 70 mμ in diameter. ×14,000. (Reproduced from Epstein, 1958b, by courtesy of the Editor of the* British Journal of Cancer)

Fig 5 *Group of bacterial virus particles air-dried and lightly shadowed with palladium. The hexagonal, pointed head and straight tail can be distinguished. ×150,000*

Fig 6 *Adenovirus particle (left) at high magnification (×700,000) with (right) a photograph of a model of an icosahedron in the same orientation and having 252 surface units. (Reproduced from Horne* et al. *1959, by kind permission)*



Figs 9 - 14

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specific enzymes (Epstein 1958*c*, Holt and Epstein 1958). The samples were then incubated at 37° C for two hours at pH 9; after this some of the samples were incubated for a further two hours in ribonuclease (RNase), some in deoxyribonuclease (DNase) and some in enzyme-free control fluid. After this all samples were prepared for sectioning for electron microscopy.

On examination it was found that the incubation procedures had caused some distortion of the particles. Nevertheless those which were treated with RNase retained their dense nucleoids (Fig 11), as did the control particles which were only exposed to enzyme-free medium. In marked contrast the nucleoids were digested in the particles incubated in DNase (Fig 12) thus establishing that the adenovirus contains much nucleic acid of deoxy type localized within its nucleoid (Epstein *et al.* 1960).

The nature of the nucleic acid was confirmed by combined electron microscopy and cytochemical staining as follows: when ribonucleic acid (RNA) containing structures are stained with acridine orange and examined in ultraviolet light (UVL) they exhibit an orange-red fluorescence, while similarly stained deoxyribonucleic acid (DNA) containing structures have a yellowish-green colour (von Bertalanffy & Bickis 1956, Armstrong 1956) and these responses are specifically diagnostic if they are abolished by treatment with the appropriate nuclease before staining. Particle-containing samples of adeno pellets were therefore smeared on glass slides or prepared for electron microscopy. The composition of the samples was checked in the electron microscope and the material on the slides, thus known to consist of virus particles (Fig 2), was then fixed, incubated at pH 9 and stained with acridine orange. On examination in UVL the specimens gave the characteristic green fluorescence shown by DNA and this definitely indicated the presence of such nucleic acid since the colour was typical and, more important, since it was abolished in those samples treated with DNase before staining. Similarly prepared samples which were incubated with RNase or control medium before staining did not have their green fluorescence affected in any way (Epstein *et al.* 1960).

Exactly the same type of result has been obtained with the Rous virus (Epstein & Holt 1958); particles with intact nucleoids were found after incubation in control medium (Fig 13) whilst digested nucleoids were seen in those particles which had been exposed to RNase (Fig 14). That this tumour virus depends on nucleic acid of ribose type for its genetic continuity was confirmed by checking preparations for their virus content with the electron microscope (Fig 4) and then applying acridine orange staining for nucleic acids, just as was done in the adenovirus experiments already described. A typical orange-red RNA fluorescence response was obtained on direct staining and was found to be abolished in those preparations where RNase had been applied before the staining (Epstein & Holt 1958).

Discussion

In this brief survey an attempt has been made to illustrate the ways in which the electron microscope can be used in the study of viruses, and to emphasize that its usefulness is greatest when it is integrated with other techniques and methods. The electron microscopy of virus-infected cells has purposely been avoided, since, being more a question of cells than viruses, it clearly falls outside the scope of the present allotted subject.

The results which have been described and discussed may appear at first sight highly academic and devoid of practical use. But, as with all research into basic questions, it must not be forgotten that the understanding of fundamentals leads inevitably to an understanding of problems stemming from them. The structure and nucleic acid content of a given infective or tumour-causing virus is of vital importance in determining how such an agent will behave and multiply, and

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Fig 9 *Rous virus particles prepared for electron microscopy directly after fixation. The double outer limiting membranes and dense nucleoids can be seen.* ×*200,000.* (*Reproduced from Epstein. 1958b, by courtesy of the Editor of the* British Journal of Cancer)

Fig 10 *Rous virus particles after incubation to reveal the fine membrane between the nucleoid and the viroplasm.* ×*200,000.* (*Reproduced from Epstein & Holt, 1958, by kind permission*)

Fig 11 *Adenovirus particles prepared after incubation at pH 9 for two hours at 37° C followed by a further two hours' incubation in RNase. Although some swelling of the particles has occurred, their nucleoids are intact.* ×*100,000.* (*Reproduced from Epstein* et al. *1960, by kind permission*)

Fig 12 *Adenovirus incubated as those shown in Fig 11 except that DNase was used in place of RNase. The nucleoids have been digested leaving an empty space in many particles.* ×*100,000.* (*Reproduced from Epstein* et al. *1960, by kind permission*)

Fig 13 *Rous virus particles after incubation for two hours at 37° C in control medium. The particles appear extracted but their nucleoids can be clearly distinguished.* ×*105,000.* (*Reproduced from Epstein & Holt, 1958, by kind permission*)

Fig 14 *Rous virus treated exactly as that shown in the previous figure except that RNase was present in the incubation medium. The nucleoids have been removed and the particles appear slightly swollen.* ×*105,000.* (*Reproduced from Epstein & Holt, 1958, by kind permission*)

once the intimate biological nature of viruses begins to be comprehended, the manner in which they bring about the changes responsible for the manifestations of disease inevitably ceases to be a complete enigma.

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Meeting May 11 1961 at the National Institute for Medical Research, Mill Hill, London

The following demonstrations were given:

The Influence of Metabolic Analogues on Virus-infected Cells
Donna M Chaproniere

Interferon and Tumour Viruses
A C Allison & M Oxman

Studies on the Possible Persistence of Sendai Virus in Mice
L Sawicki

Observations on Trachoma Virus
Celia Fildes

Recent Studies on Interferon
S Baron & A Isaacs

The Identification of Arthropod-borne Viruses in Tissue Culture
J S Porterfield

Growth of *Myco. lepræ murium* in Tissue Culture
Elizabeth Garbutt, Joan M Barham & R J W Rees

Attempts to Grow *Myco. lepræ murium* in Cell-free Bacteriological Media
P D'Arcy Hart & R Valentine

Immunological Studies in Leprosy
K R Chatterjee, Rosemary D Tee & R J W Rees

Cytochemical and Fine Structural Features of Virus-infected Cells
J A Armstrong & Janet S F Niven

Gamma-globulin Metabolism and Antibody Production in Mice Bearing Transplantable Myelomas
J H Humphrey & J L Fahey

Differences in the Histological Pattern of Fluorescent Staining by Human Auto Antibodies
B M Balfour & J S Beek

Production of a Slow Reacting Substance as a Result of Antigen Antibody Reaction in the Rat
H J Rapp

The Proteins Produced by some Transplantable Myelomas of Mice
B A Askonas

International Standards for Biological Substances
J W Lightbown, D R Bangham & L Ward

Development of Serum Proteins in Fœtal Primates
D E H Tee

Exchange of Serum Proteins to and from the Primate Fœtus
D R Bangham, K R Hobbs & D E H Tee

Penicillinase and the New Penicillins
R Novick

Biosynthesis of False Proteins by Bacteria
J Mandelstam

Resistance and Sensitivity to the New Penicillins
P Sneath & D Swallow

Mechanism of Action of the New Penicillins
H J Rogers, H R Perkins & J Jeljaszewicz

Section of Psychiatry

President Noel Harris MD

Meeting March 14 1961

Transatlantic Discussion : The Place of Psychiatry in Medicine To-day [*Abridged*]

Chairman David Stafford-Clark MD FRCP

OPENING STATEMENTS

Dr David Stafford-Clark (*London*)

Modern psychiatry has an indispensable contribution to make to the relief of suffering; in fact, the essental link between psychiatry, general medicine, surgery and obstetrics lies in the ultimate impossibility of treating states of mind apart from states of body, or states of body apart from states of mind. If psychiatry had made no greater contribution to the balance and equilibrium of the general medical curriculum than to endorse and emphasize this single fact, its contribution would still be invaluable; for it has all too often been the assumption in the past that, while bodily states have to be exhaustively observed and meticulously studied, mental states can be either taken for granted or dismissed as irrelevant, in the training of the doctor.

Teachers of medicine have come to recognize this increasingly during the past twenty-five years. Quoting exclusively from non-psychiatric sources one might select an observation by a former President of the Royal College of Physicians, who said in May 1952: 'There can hardly be any bodily state which does not to a greater or less extent influence the mind, and there can hardly be any state of mind which does not in its turn influence in some degree the functions of the body' (Brain 1952).

Referring to the instruction of the medical student Woodger (1956) wrote:

> When we look at the list of those basic sciences to which the work of the first year is devoted, we are astonished to find that not *one* of these sciences deals with human beings as persons or as members of societies. In other words no psychology or sociology is included. The only sciences taught as basic sciences are physics, chemistry and biology.... The effect of the pre-clinical training is all in the direction of reinforcing the impression left by the first-year studies. Anatomy is largely an affair of corpses that cannot talk. Physiology is frequently taught from the point of view of a dogma which has been expressed by William Bayliss in the following words: 'The aim of all physiological experimentation is to express vital processes in terms of physical and chemical laws. We call this "explaining" them.'

This was written in 1956. Admittedly the wind of change has begun to blow through medicine as well as elsewhere. It is exemplified both by the work done in medical schools on both sides of the Atlantic in psychosomatic teaching and research, and by the passage in the United Kingdom of the Mental Health Act, 1959, whereby mental illness is legally recognized as benefiting from and requiring an identical approach to that traditionally accorded general medicine and surgery: informal admission and discharge and the abandonment of the segregation and geographical and social isolation of the mentally ill.

A recent report of the World Health Organization (WHO 1961) is devoted to 'The Undergraduate Teaching of Psychiatry and Mental Health Promotion'. This report echoes and endorses something I myself wrote in 1953, that psychiatry has in fact a vital role in medicine to-day. Not only has it its own indispensable technical and special contribution to make to the training and subsequent clinical practice of every doctor: but even more important, in the increasing technical specialization of scientific medicine and surgery, it must continually re-emphasize and help to meet the need for an understanding of human relationships and feelings, and the way in which they both affect and are affected by physical health or disease, as indispensable to the properly trained doctor.

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Dr M Ralph Kaufman (*New York*)

Modern dynamic psychiatry plays a dual role in medicine to-day. As a sub-specialty of medicine it deals in the broadest sense with a group of syndromes that have been categorized as nervous and mental diseases. In this area the psychiatrist functions as any other specialist in medicine. He diagnoses in terms of current nosological tenets and engages in various types of therapeutic endeavours related in most instances to his theoretical and pragmatic frames of reference.

The other function of psychiatry may be of even greater significance to medicine, and that is psychiatry as medical psychology in the broadest sense of the term. This aspect of the discipline draws upon all the basic sciences related to medicine, with particular emphasis on the behavioural sciences. It is in this area, which deals with the patient as a person in an ecological unity involving his heredity, constitution and total life experiences in relationship to his environment and interpersonal relationships, that psychiatry may contribute most to medicine as it is practised to-day.

According to this formulation psychiatry can and has contributed to a more fundamental understanding of the patient as a person. In this sense it is relevant to all aspects of medicine both as an art and a science. Psychosomatic medicine and social medicine are attempts to integrate this aspect of psychiatry into medicine.

Sir Robert Platt (*Manchester*)

I speak as a physician who had little training in psychiatry, but who always tries, in diagnosis and treatment, to take into account the state of the patient's mind. I think that psychiatry has another role which we must not forget, namely that Freudian psychology has enlightened the whole of human thought during this century and so something of Freudian psychology should be learned by any educated man.

Just to throw in a few controversial thoughts to which we might come back later, I suggest that something might be said about the place of the psychiatrist in medicine to-day which I take to be something slightly different from the place of psychiatry.

Secondly, I think we might disagree on the extent to which psychiatry is a science and to be regarded as a science. I do not think that this is wholly irrelevant because the extent to which psychiatry is acceptable to our more mechanistic colleagues rather depends upon its acceptance as a science.

Thirdly, to what extent do we accept psychological factors as causative in psychosomatic disease? We surely, reasonably enlightened people that we are, accept psychological factors as exacerbating, and having a tremendous influence on disease. Do we accept them as causative of somatic disease?

And finally, if we all agree that more psychiatry should be taught to medical students, then do we agree on what should be taught and how it should be taught?

Dr Lawrence E Hinkle Jr (*New York*)

It is my belief that the training of every physician should provide him with a basis for understanding the behaviour of the people who will be the objects of his care throughout his lifetime, and a comprehension of the way that a man's adaptive reactions may affect his health. The lack of this knowledge can profoundly hamper diagnosis and can make it extremely difficult for the physician to establish an effective therapeutic relationship with his patient.

We should present to the medical student the fundamental information about the social and cultural determinants of behaviour and about the mechanisms of conditioning, of learning, of group interactions, of interpersonal relations and of psychodynamics, as these have been defined by the cultural anthropologist, the sociologist, the neurophysiologist, the psychologist and the psychiatrist. I look forward to the day when a basic course in social and behavioural science, providing a succinct summary of this information so far as it is pertinent to medicine, will become an integral part of the medical curriculum.

I regard psychiatry as a clinical science rather than a basic science. I see it as that segment of clinical medicine which is concerned with the aspects of human illness which are manifested primarily as disturbances of mood, thought or behaviour. Training in psychiatry is, of course, an essential part of clinical medicine. Physicians who are not psychiatrists must have the ability to recognize these manifestations of mood, thought and behaviour which are regarded as 'abnormal' and as manifestations of illness; and they need to understand the special measures which may be required for the treatment of such phenomena. But they must also have a broad understanding of human behaviour, and especially of that behaviour which is regarded as 'normal' or healthy in their own society.

Yet, I would not separate the psychiatrist from the rest of clinical medicine. Instead, I would integrate him more closely with it. The psychiatrist needs a considerable knowledge of medicine, the physician requires an equal knowledge of

psychiatry, and both need to share one another's knowledge and skills in dealing with the same patients. It is not reasonable to segregate psychiatric patients and psychiatric practice as if they existed in a world apart from the world of general medicine and of no concern to it. I see the psychiatrist as a physician whose point of view is fundamentally no different from that of other physicians, who works side by side with his colleagues in the community and in the hospital, sharing closely with them his special knowledge and understanding, and being a specialist only in that he is primarily concerned with the treatment of certain manifestations of illness. I see the psychiatric patient, like the surgical patient or the obstetrical patient, as being treated in a special segment of the hospital only when the manifestations of his illness are such as to require the use of special facilities for his care. At other times and under other circumstances we must recognize him for what he is: the same person as the medical patient or the surgical patient, but with another manifestation of his illness temporarily outstanding.

Professor Denis Hill (*London*)

I believe the most important goal before us is the acceptance by every doctor, at the time of his graduation, of the role of psychic function as a major determinant of health or disease. I hold that psychic and somatic functions cannot be considered as belonging to two separate unrelated systems within the organism but both are aspects of the one individual and both are closely interrelated with one another and with the environment. However, just as physiological functions can only be described in physiological terms and have their own reality, so psychological functions can only be described in psychological terms and have an equivalent and equal reality. This has to be accepted. It will be a major task for the future to educate our students to the realization of the reality of psychological functions within the human organism and within society, and their relevance to biological adaptation in health and disease.

In Britain there has been in the last twelve years a dramatic and increasing change in the psychiatric scene. A reintegration of psychiatry in medicine is taking place and psychiatric wards and units are being opened in many general hospitals. Contacts between psychiatrists and general physicians are now much closer and the psychiatric patient can share with the physically sick patient on an equal footing the benefits of the Health Service. The opportunity to put psychiatry on display before the medical students is increasingly given but still far less so than in most schools in the United States.

We psychiatrists, however, have to admit that we are not united ideologically among ourselves. There is still a sharp antithesis between those who adhere to an organic-causal approach to all mental functions and those who favour a psychosocial approach. The former despise psychological determinism; the latter have no interest in cerebral mechanisms. This antithesis is, I believe, a false one, but it is dying hard. It is far more difficult for the student of medicine to resolve this difficulty if he meets it only late in his studies. It is something which must be tackled at the beginning because the problem involves considering fundamental questions about man's nature. This evokes ideas which may run contrary to all his previous training and his attitudes acquired from his parents and his school. The medical curriculum, orientated as it is on a disease-system basis, with great emphasis on physical and chemical processes and ætiological in approach, further protects the student from contact with the realities of psychological life. Many doctors, educated in the traditional way, are more unaware of their patients' emotional life than the educated layman. They often appear to have a scotoma for this aspect of the human organism – a scotoma which is a cultural product of our medical education.

My thesis then is that the place of psychiatry in medicine will depend in the future upon how our medical students are educated.

DISCUSSION

Dr Stafford-Clark suggested that present methods of undergraduate education introduced, almost unnoticed and at an early stage, an organic *versus* functional bias. There was a danger of equating the functional with the imaginary, derisory and unimportant.

Sir Robert Platt said that, since Hippocrates, it was traditional to recognize that all illness had psychological aspects. He felt that physicians should not hesitate to call in psychiatric colleagues for consultation; but that they should whenever possible keep their patients under their own care.

Dr Hinkle advocated better psychiatric education of the physician, so that increased skill in his management of the psychological aspects of physical illness might be accompanied by greater confidence in his judgment as to when best to call in the psychiatrist.

Dr Kaufman remarked that in his hospital physicians did not lose their patients to the psychiatrists whom they called in consultation. He stressed the complementary roles of psychiatrists and other specialists in a general hospital team.

Professor Hill advocated the appointment of liaison psychiatrists to each of the several departments of a hospital, with responsibility to the chief of that department.

Sir Robert Platt was in favour of the admission of selected medical cases into psychiatric wards when the investigation or treatment of their symptoms required it.

Dr Hinkle thought that the choice of ward in admitting a patient should depend on who had the therapeutic techniques most likely to help at that time. Schizophrenics might sometimes need to be admitted to medical or surgical wards.

Sir Robert Platt pointed out that the selection of cases for referral depended also on the interests of the individual psychiatrist.

Dr Hinkle said that the question was what part personal factors played in the course of the illness and whether they could be manipulated in such a way as to benefit the patient. In conditions such as ulcerative colitis there was often a strong element of adaptive disturbance as part of the illness, but attention to such factors was not always therapeutically effective.

Dr Kaufman said that in a random sample of 253 admissions to all wards of a general hospital, there was a diagnosable psychiatric condition in 66·8%. Over 1,000 general hospitals in the United States now admitted psychiatric patients directly. Of half a million psychiatric admissions in 1958, 257,000 were admitted directly to general hospitals. These figures emphasized the importance of physicians having a knowledge of psychiatry.

Dr Stafford-Clark expressed the view that all doctors should, in their preclinical and early clinical training, receive instruction in the fundamental mind-body relationship, personality development, and the repercussion of emotion upon autonomic and endocrine function.

Sir Robert Platt urged the introduction of psychological concepts to the student early, before his mind became set in the mould of mechanistic thinking. Real instruction about the mind must be given in the preclinical course, and some psychiatric training must run throughout the whole of the clinical period.

Professor Hill felt that the medical student should, during his biology course, be introduced to the idea that animals have social needs, and should study animal behaviour and ecology and comparative ethology. The student should not be given the idea that there were two kinds of psychology, one leading from Pavlov through Hull to cybernetics, this somehow being connected with neurophysiology, and the other ego-orientated and derived from Freud.

Dr Kaufman advocated the teaching of psychophysiology by pharmacologists and physiologists during courses in their subjects, and of psychiatry by physicians in the normal course of their clinical practice. If psychiatry was taught only by psychiatrists, students would feel that there were two kinds of medicine. He deplored the existence of such double standards.

FINAL REMARKS

Professor Denis Hill

I would agree with Dr Kaufman that it would be an ideal world in which the behavioural sciences and the relationship between behavioural and other fields of basic science could be taught by the experts in these sciences. If the neuropharmacologist could teach his bit and the physiologist his bit, this would be ideal; but, unfortunately, this cannot happen. It certainly cannot happen in this country because they are not equipped to do it, and therefore other people have to do it. But I do agree that the more psychiatry can be taught by general physicians the better.

There is one thing we have perhaps left out, and that is the contribution that psychology and psychiatry can make towards the personal attributes of the doctor and one of the things we can add to the doctor whatever his work may be in the future. Contact with psychiatry can bring about an understanding and a supporting attitude towards patients, and can teach doctors how to let patients talk about themselves without fear of censure, ridicule or betrayal. Further, we can perhaps tell doctors, and teach them, how to elicit important data about life experiences. Even more important is the capacity to combine these personal qualities in the doctor with the capacity for objective appraisal of the patient's capacities, attitudes, and motivations. How can we do this? I think that students require an adequate contact with a sufficient number of patients at the interpersonal level, with patients of all kinds, with children, their mothers, with adolescents, with adults, and the aged. Our students should be exposed to all forms of human suffering, personal disaster, and personal malfunction as well as being close to normal human beings at all stages of their development. As psychiatrists we can help by precept and example. The student should see psychiatrists at work. Lastly, the student must have at his disposal a sufficient range of knowledge about individual differences, about human needs, and about human motivation. This is all in addition to his knowledge of psychopathology and in addition to his formal knowledge about psychiatric illnesses.

Dr L E Hinkle

It is undoubtedly important that all the faculties of a medical school should take into account what we know from the behavioural and social sciences, just as they take into account what we know from chemistry, physics and biology. But in addition to this, it is necessary that we have, in the early years of the medical curriculum, a course directly concerned with teaching medical students that which is relevant to medicine from both the behavioural and the social sciences. Some of this is simply basic information; but part of it demands a certain selectiveness on the part of those who teach it. It is necessary to combine information from the social sciences and from experimental and clinical psychology, with information from physiology and clinical medicine, to show how

these are related. By the same token, it is necessary to make clear that there are some bodies of information which can be profitably studied from several points of view. For example, there are certain dynamic mechanisms which can be understood both in the terms of psychodynamics and also in terms of experimental psychology, and both of these points of view should be presented to the student. The time has long since passed when we should take a deprecating attitude towards the sciences which deal with the very difficult body of social and psychological information. They have come a very long way, and they have many things to tell us which can be of help to us, even though they have not attained any final answers. In my opinion the 'basic science' course in this area would not be psychiatry, but would be behavioural and social science as directed at medicine with a view to providing all physicians with some of the information in these areas which we know they will need greatly later in their careers.

Sir Robert Platt
I would like to say just a little more on the question of psychiatry and psychology as science because there still is a great tendency to judge science by its power to predict by experiment, and by its ability to measure phenomena and express them numerically. I think Dr Hinkle rather begged the question by calling psychiatry a clinical science, because the very people who will say that psychiatry is not a science at all will also say that the clinician is not a scientist, and they may be right. It does help me to think that psychiatry and psychology have been greatly blessed by *not* trying to measure things. They have often gone astray when they have tried to measure things because they find themselves measuring either the trivial or the irrelevant. It helps me to feel that a science can be judged in one of two ways: by its predictable experiments and by its measurable phenomena, or by the closeness of fit between the theory and observable fact. The latter, surely, is the kind of science that both Freud and Darwin were writing about. Darwin did very little experimental work. His thesis rests upon the fact that the more you look into it the more you find that it explains observable fact, and I think psychiatry can be judged in that way. I do not think that it has gone as far as Darwin but it is going that way.

Dr M Ralph Kaufman
Perhaps I exaggerate a little for effect when I say that no psychiatrist should teach psychiatry. What bothers me about the psychiatrist teaching the medical student is that if the student identifies himself with the professor of medicine (which he does more often than with the psychiatrist), and the professor of medicine either ridicules or does not pay any attention, then the effect of the teaching is lost. At the present time, the American Medical Association is involved in setting up a series of conferences which will encourage the 200,000 practising physicians to accept their responsibility for every aspect of psychiatry in the patient that comes into their office, and take an interest in our State or special hospitals. It is hoped that in this way, over a period of years, psychiatry will be given a kind of priority in relation to the integral practice of medicine. To us who are working on this particular plan it seems to be a giant step forward to placing psychiatry in its proper perspective.

Dr David Stafford-Clark
The contribution of psychiatry to a fuller understanding of the principles and practice of medicine is ultimately to underline a final and fundamental truth – the wholeness, dignity, and infinite value of the individual man or woman.

The Honorary Officers of the Section are indebted to Messrs Smith, Kline & French for the provision of the transatlantic link.

Meeting June 13 1961

Paper

The Illness of Vincent Van Gogh

by R E Hemphill MA MD DPM (*Barrow Gurney*)

There have been many interpretations in books, films and plays of the career and illness of Vincent Van Gogh. Although his life is well documented contemporary medical records are slight. He was never examined by a neurologist nor a leading psychiatrist. The young Dr Rey had no special experience and only cursory records were made by the doctors of the country asylum at St Remy. Yet it is possible by referring to his letters and the accounts of his friends, and examining the development of his art, to arrive at a reasonable estimate of his character and the probable nature of his illness.

Two facts are remarkable: apart from his brother Théo no one regarded Van Gogh as a significant artist during his lifetime and he sold

only one picture, 'The Red Vine' in 1890; in spite of this, by his humanity, energy, and expressiveness, he engaged and retained the interest of relatives and friends. To some of these he revealed in letters his every thought and the daily changes of his emotions and hopes. Although hot tempered, latterly alcoholic, poor and unsuccessful he was never considered to be of bad character, a criminal, a tiresome drunk or a dangerous madman. When the crises of his illness had subsided doctors, nurses and friends were always ready to give him liberty and material help, such was the impact of his personality upon them. Against this background he stands out as an exceptional and sincere man with a great capacity for friendship but who suffered from mood swings and, in the last two years, epileptic fits.

A number of hypothetical diagnoses have been made. The most important were schizophrenia, psychopathic personality, temporal lobe epilepsy and cerebral syphilis. These have been discussed fairly fully by Kraus (1941) and Gastaut (1956). Of schizophrenia and cerebral syphilis I find no evidence. His relationships with friends and indeed his character exclude psychopathy and the episodes of antisocial behaviour were due entirely to illness or alcohol. Temporal lobe epilepsy has been argued persuasively by Gastaut but this diagnosis is too narrow to explain the wide psychiatric disturbances.

In my opinion Van Gogh was a manic depressive who developed confusional episodes and fits in the last two years of his life due to the toxic action of thujone, the active agent of absinthe, to which he had become addicted. The evolution of his illness may be observed as his life history is studied.

He was born on March 30, 1853, at Groot-Zundert where his father was pastor. He was the eldest of six. His beloved brother Théo was four years younger. His mother was a talented amateur artist and his paternal uncle a picture dealer in the firm of Goupil. One sister spent many years in a mental hospital, probably for schizophrenia. There is no other known history of mental illness or epilepsy. As a boy he was conscientious and solitary with a love of landscape.

On leaving school at 16 he was apprenticed to Goupil's in Brussels and in 1873 began the series of letters to Théo which he continued with slight interruptions until his death. Théo entered the firm about 1873 and Vincent, apparently a good salesman, was transferred to the London branch. About this time he started to draw seriously but without the hope or intention of becoming an artist.

In 1874, following the rejection of a proposal of marriage by Ursula Loyer, with whose parents he lodged, he became depressed and returned to Helwirt, his father's parish. The next year he returned to Goupil's and worked in both London and Paris. 'Demoralized, ill at ease and depressed', he was dismissed for indifferent work. He recommenced work the following January but was finally sacked.

In April 1875 he wrote 'peace of mind returned to me'. He decided to become a painter but in order to earn his living he obtained a post at a small school at Ramsgate. This school failed. He felt drawn to religion and in July joined the Rev. Jönes at Isleworth as a preacher. By all accounts he was excited and eloquent and was in fact dismissed. He returned to his home at the end of the year eager to become a pastor. He prepared for matriculation at the University of Amsterdam, supporting himself by working in a bookshop.

Vincent's letters show him to have been highly intelligent, and he was certainly energetic and well read for eventually he spoke and wrote quite fluently in four languages. Yet in July 1878 he abandoned his study for the University saying that it was beyond him, that he was worn out and he talked of suicide. In November 1878 his energies came back. He now became an unqualified preacher in the poor mining district of the Borinage. Moved by the sad state of the miners, he lived like them, gave his clothes away and paid visits unwashed and unkempt. He obviously was an embarrassment to the church and he was sacked. During this time he was very active and made many drawings of peasant life around him.

During 1879 he was depressed. He wandered throughout the country, a vagabond and miserable, unable to work or settle. He wrote 'it was in the depths of misery I felt my energy return, whatever happens I shall make good' and he returned to the Borinage for a while to draw. In that year brother Théo decided that he would devote himself to Vincent and thereafter maintained him from his earnings.

In order to perfect his painting technique Vincent joined the Brussels Art School, but finding the teaching sterile he returned to Etten where his father was now pastor. There was then the incident of his refusal by Kee Vos, a widowed cousin.

In 1882 there was a period of elation when he quarrelled with his cousin, Mauve the painter, at Antwerp and started freelance painting. There followed the famous incident of Sien. She was a prostitute, an alcoholic and pregnant. He called her Sien, signifying that she was his own, and devoted himself to her and her children. In September of the next year he became depressed, abandoned Sien, left the Hague and wandered through the country with a bundle, living rough and sleeping out. He travelled in the desolate

area of the Drenthe and returned at the end of the year to Nuenen, his father's new parish. At this time he painted dark still-life pictures and dark portraits. He remained there for two years.

His life with the prostitute Sien as well as his desertion of her seem to be out of keeping with the character of the would-be evangelist but his behaviour can be explained by a hypomanic state when he idealized the woman and hoped to reform her, followed by depression, hopelessness and feelings of guilt when he abandoned her and her children, having lost the capacity for positive feeling.

In November 1885 he went to study at Antwerp and was impressed by the dramatic and emotional use of colour by Rubens whose paintings he saw for the first time. He was attracted by the Japanese colour prints which were now making their appearance in Western Europe. Unsettled, he moved to Paris to stay with his brother Théo and remained there from March 1886 to February 1888. He formed friendships with the group of modern painters that included Toulouse-Lautrec and Gauguin. There were wide fluctuations of mood and activity and some of his paintings show a new use of colour which was quite startling. Théo wrote that from time to time he seemed a changed man, sometimes intolerable and at other times gentle as he used to be. Vincent wrote that 'a spring-like poetic feeling' enveloped him and that he noticed his palette suddenly became brighter.

In February 1888 he travelled to Arles, there to live and paint. This was not in search of the sun as novelists have suggested but to seek a European landscape resembling that of the Japanese colour prints. He took rooms in a house in Place Lamartine which he called the Yellow House, yellow being the colour that indicated friendship in Japanese. There he painted many of his best-known pictures of harvests, sunflowers and local portraits. At first he wrote with great optimism that he was in 'a turmoil of work' but in July there was a period of depression. He wrote 'I threw myself body and soul into my work. If the storm inside me growls too lively I drink a glass too many to stun myself. This is madness when I consider what I ought to be'. During the year there were periods of great activity when he scarcely had time to eat and in one week it is said that he lived on 23 cups of coffee and a little bread. In the autumn he evolved the idea of making the Yellow House a centre for painters. He invited Paul Gauguin, who was then the centre of a circle at Pont Aven, to join him and, with Théo paying the fare, Gauguin arrived at Arles. Gauguin, so dissimilar from Vincent, quarrelled with him at once. He encouraged him to drink and visit the brothels and would not put up with his frugal living. On Christmas Eve 1888 there was a quarrel. According to Gauguin's unreliable story (1952), Vincent threatened him with a razor. Gauguin went to a hotel and in the night Vincent cut off part of his ear, parcelled it up and deposited it with the prostitute Rachel at the No. 1 brothel in Arles. The story of the ear has been much romanticized but the truth from contemporary records, as related by Doiteau (1940) is as follows: Vincent cut off the upper part of his left ear, which appears as the right in the self-portrait painted from the mirror. He parcelled it up and brought it to Rachel. Terrified of trouble she gave it to Madame Virginie, the proprietress, who in her turn gave it to the police. Next day, too late to be sutured on to Vincent, it was brought to the hospital. Dr Rey kept it in spirit until the autumn of that year. His successor threw it out.

Vincent retained no recollection of the event. It occurred probably in a post-epileptic or alcoholic delirious state. He was admitted to the Observation Ward at the General Hospital under Dr Rey, a young interne, who noted that he had a 'sort of epilepsy'. Vincent was apparently in a state of excitement and confusion with terrifying hallucinations of sight and hearing and a great agitation – what may have been delirium tremens. For several days he was ill but on January 1 he was well enough to go out with a friend.

The following is a record of the clinical history in chronological order:

On the night of Christmas Eve 1888 he cut off his ear and was admitted in a state of delirium to the hospital. On January 7, 1889, he was discharged but experienced what he called 'surexcitation'. This seems to have been hypomania. On January 30 he was in a state of excitement. On February 8 he was confused, thought he had been poisoned and was readmitted to hospital. On February 20 he improved and was able to write to his brother Théo. On February 28 he became confused and wild and was put back into the cells. On March 19 he was better and wrote again to Théo, but apparently there was another phase of excitement. On March 23 the painter Signac visited him and took him out to the city, whereupon he drank turpentine with immediate relapse. On March 27 he was calm.

These attacks seem all to have been similar with excitement, terrifying hallucinations and wild behaviour followed by confusion. On each occasion he left hospital he drank absinthe and this seems to have provoked a recurrence. On May 9 he decided to enter St Remy Hospital as a voluntary patient. There he was treated with great consideration and in spite of his erratic behaviour granted a room to himself and opportunities to paint.

He began to paint with great fervour. On July 6, 1889, on parole, he went into Arles, drank and

immediately had a convulsion and a fall. In August he was working and painting. In September he was extremely active, in a state of hypomania. In October he had settled, and was granted permission to paint outside the asylum. At Christmas there was an episode of drinking. On February 20, 1890, he went for two days to Arles, began to drink, became confused and wandered, and for the next two months had episodes of excitement with night terrors and hallucinations. In April, in a state of depression, he attempted suicide by swallowing his paints. On April 29 he was brighter but still depressed. He then felt that he was becoming normal because he wrote that he could no longer tolerate the company of patients and persons around him. His brother Théo arranged for him to lodge at Auvers, near Paris, under the supervision of Dr Gachet who was a well-known amateur artist and friend of artists.

Vincent left St Remy and spent four days in Paris. On May 21, 1890, he arrived at Auvers. On July 6, no longer drinking, he visited Théo at Paris. Friends noticed that he was sad and seemed unsettled. On July 8 he painted the last 'Cornfield' subject with its troubled skies and sinister crows. He said it expressed 'solitude and sadness'. The end was now inevitable as the signs of depression were not recognized by those around him. On July 14 he watched the National Day celebrations and painted a strange picture of the town hall. It is decorated with flags but the scene is devoid of gaiety and the square is empty of people. On July 27 he shot himself and died on July 29. Just before his death he wrote an incoherent letter to Théo and his last words were 'will this misery never end?'

Dr Felix Rey attended and befriended him from the time he was first admitted to the hospital at Christmas 1888 until Rey left for a post in Paris about six months later. He considered that he was suffering from 'a sort of epilepsy with hallucinations and episodes of agitation and confusion provoked by alcoholic excesses'. He gave this diagnosis to his chief, Dr Urphar, head of the hospital at Arles and to Dr Peyron of St Remy, to Théo and to Vincent. No other clinical diagnosis seems to have been made in Vincent's lifetime. He was treated by bromide in heavy doses and by the withholding of alcohol.

His mental illness, complicated by alcoholism and a form of epilepsy, was a manic depressive psychosis. The following extracts from his letters to Théo show this clearly:

July 1880: 'The traveller after many wanderings and after being tossed on a stormy sea arrives at last at his destination. He who seemed good for nothing and incapable of performing any task finished by finding a place suitable for him and capable and full of activity he turns out to be quite otherwise than he seemed at first sight. . . . One who is inwardly tortured by a desire for action who does nothing because it is impossible for him to do anything, because it is as if he were imprisoned within something. . . . When sympathy returns life is born again.'

1888: 'If you are healthy you must be able under those conditions to work the whole day on a single piece of bread and still have the strength to smoke and drink your glass. You can feel the stars and the infinite above so that in spite of everything life is almost enchanting.'

July 1890: 'I have started to work again but the brush nearly drops from my hand. Paintings represent enormous stretches of cornfield under a troubled sky and I have not hesitated to express the feeling of sadness and utter solitude.'

In his letters to his brother and to Bernard he refers repeatedly to changes of mood, and fluctuations between elation and anguish were noticed by Théo. Dr Rey wrote 'just after each crisis he had a great urge to paint and an eye very acute, and he thought he could reach heights of his art that had seemed unattainable'.

There is no evidence that he touched alcohol before he arrived in Paris. About 1886 he began to drink heavily and his portrait by Toulouse-Lautrec shows him sitting at a table staring over a glass of absinthe. There is a suspicion that he had fits during 1887 and in the winter of 1887–8 already some major fits were observed. During the period of 1889 undoubtedly some of the fits were prolonged and accompanied by convulsions. In one of the phases he showed a retrospective memory very suggestive of a temporal lobe disturbance. He wrote 'during my illness I recaptured in my imagination every room in the house at Zundert, every path, every plant in the garden, views of the surrounding country, the fields, the neighbours, the cemetery, the church, our garden, the kitchen garden behind, everything down to the magpie in the tall acacia in the cemetery'.

The mental effects of the old absinthe were well known. Numerous writers and painters described them in nineteenth century France. Alfred de Musset wrote a poem 'To Absinthe'. The old absinthe was introduced into France by North African troops in the 1840s. They believed that it prevented fever. It was made from artimesia, the volatile oil of which was thujone, in 40–80% alcohol. Thujone produces marked excitation of the autonomic nervous system and over-indulgence is said to produce manic states and hallucinations. Sollmann (1948) and Meyers (1929) discuss its pharmacology and effects.

In France absinthe drinking created a great social problem because of the eventual mental deterioration it caused. In 1912 the sale of real

absinthe was forbidden by law and a substitute introduced. In 1914 absinthe was prohibited altogether but in 1922 it was licensed for sale containing 40% alcohol plus 2 g of essence per litre after extraction of thujone.

There is clear evidence that Vincent took increasing quantities of old absinthe and that in the course of the last eighteen months of his life this was accompanied by fits with hallucinations of a kind that have been well described by writers as occurring in absinthe drinkers. When allowed to go into Arles from hospital he frequently drank absinthe, provoking further fits and confusion, sometimes prolonged. Vincent's fits seem to have been controlled by bromide and withholding alcohol which would be indicated for absinthe intoxication but not likely to be effective in temporal lobe epilepsy. The fits seem to have subsided in 1890 and there is no indication from the written record of developing organic dementia. Yet his agitated writhing style of painting, which is marked in 1889, may have been in part due to brain disturbance. It never really changed and is as marked in portraits as in southern landscapes. This will be well seen by comparing the strange portrait of two children of June 1890 with any of the portraits before 1889.

There is no evidence of schizophrenia or of psychopathic personality. On the contrary his personality was warm and friendly. He was intelligent and loyal. He tried to repay kindnesses and even bothered Théo to purchase an Old Master engraving which he thought Dr Rey would like. There was never any phantasy formation and his writings are lucid and logical. He was deeply moved by unhappiness and misery around him and it is this no doubt, rather than evangelical urge, that caused him to work amongst the poor miners. Throughout his life he had the compulsion to communicate and exteriorize his feelings. It would appear that words were inadequate to express them and it was on this account that he became a painter. He perfected his technique by studying hard at various art schools until he evolved a method of painting suitable for his emotional requirements.

Van Gogh always worked from subjects. He painted landscapes, still life, and portraits and copied other paintings. All his paintings are remarkably precise records of the subjects in front of him but transformed to express the intensity of his emotions by use of colour and the manipulation of paint. Tralbaut (1959) has reproduced a number of his pictures alongside photographs of the scenes or sitters, from which it will be seen that the formal accuracy is astonishing and that he took no liberties with the factual elements of a subject. He has left no visionary creations or purely imaginary pictures.

All of his great output (more than 800 are catalogued by Faille and many are known to have been lost or destroyed in his life) was produced in his last seven years and it is in the last four years that his technical mastery was sufficient to express his feelings. In many of those of 1888–9 painted at Arles there is a quality of agitation, with waving flame-like lines, that is suggestive of toxæmia or brain disturbances as well as supercharged emotional excitement. The trees, roads and clouds writhe and the sun burns with quivering intensity. When depressed the tones become more sombre. The last 'Cornfield' of July 1890 is in gloomy and forboding contrast to the illuminated joy of the 'Provençal Cornfield' of the previous year. The 'Church at Auvers' of July 1890 is more subdued and stark in colour relationships than usual and the last picture 'The Mairie' of July 14, as mentioned before, conveys the feeling of desolation or even of imminent disintegration.

The fluctuations of colour and style are well seen by a series of drawings, in chronological order, selected by Cooper (1955). In studies 26 and 27, made between May and July 1889, when he had fits and was confined to his room at St Remy, there is a lack of composition and of linear perspective. In No. 32, made in June 1890, the landscape is much altered as if 'nearing the final crisis of his life, his vision of nature became increasingly charged with the violence of his personal drama'. In addition to the above, the following selected pictures illustrate his development and the theory I have propounded:

Sien (1882)
Potato Eaters (May 1885)
Portrait of a Woman (December 1885)
Japonaiserie, The Tree (1886)
Le Père Tanguy (Paris period, 1887)
His Bedroom (February 1888)
The Bridge, Arles (March 1888)
Harvest (June 1888)
Sunflowers (June 1888)
The Yellow House (July 1888)
Café at Night (September 1888)
Hospital Garden (May 1889)
Superintendent of Nurses, Trabu (September 1889)
Cornfields (June 1889)
Yellow Corn (October 1889)
The Ravine (December 1889)
Road and Cypresses (May 1890)
Portrait of Dr Gachet (June 1890)
Two children (June 1890)
The Church, Auvers (July 1890)
Cornfield and Crows (July 1890)
The Mairie (July 1890)

Many artists have left self-portraits but none so many as Van Gogh. He painted 30 self-portraits and 3 sketches in the five years between 1885 and 1890, the majority in Paris and the last two at St Remy Asylum. In all these self-portraits the artist has a questioning eye and he seems to observe himself in the mirror as some depressed patients

do, looking for reassurance or endeavouring to see themselves as they feel they are. Nearly all the Van Gogh self-portraits express this uneasiness. In my view, calm is observed only in the self-portrait after he has mutilated his ear, the portrait of the man with the pipe, expressing the calm and relief that is so often observed in the depressive after an attempt of suicide.

Portraits of Van Gogh have been left by John Russell (1886), Levens, the Australian artist (1886), Toulouse-Lautrec (1887) and Gauguin (1888). Of these the pastel by Toulouse-Lautrec is regarded as the best. In all he is seen keenly observing and absorbing the world in front of him.

It is remarkable that his pictures, which so soon after his death became among the most popular romantic pictures of all time, should have been so generally misunderstood and failed to move those around him in his life. Dr Rey, who died in 1927, to the end thought nothing of them. He accepted his own portrait to please Vincent, put it in the henhouse and sold it later for 150 francs which he considered too much. In 1908 it was sold to a Russian dealer for 4,600 francs.

At St Remy, Vincent could not persuade anyone but the pharmacist to accept a painting and he only did so to ease his disappointment.

Théo appears to have believed more in Vincent's genius than in his painting. He died about six months after his brother, not of a broken heart as has been said, but of uræmia, having suffered from stones in the kidney, uræmia and pyelitis for some years. He had a psychotic episode and became suspicious and dangerous when uræmic some time before his death.

It would appear that to-day for many people Vincent's pictures show aspects of the real world as the ordinary man would like to see it, that is to say emotionally and not realistically, and that in his lifetime the public eye was still conditioned by the old criteria of visual expression and not sufficiently liberated to appreciate his work. This was soon to change, as the poet H von Hofmannsthal (1952) realized when he wrote of an exhibition in 1901, of the 'still obscure artist Vincent Van Gogh'.

It is possible that but for his cyclothymic mood swings and the cerebral effect of absinthe the intensity of his vision of the world might not have been released into his masterpieces. He was aware of the irresistible forces of his illness and may have felt this when he wrote 'we must all share in diseases. It is hardly fair to be free of them if one has lived for years in good health. I would not exactly have chosen madness if I had had my choice, but once one has had a disease like that one cannot catch it again. Perhaps it is a consolation that in spite of it I can continue to paint. Although I think squarely of accepting the role of an insane person, I do not feel that I have the strength for such a role'.

Among the extensive bibliography about Van Gogh, the most informative about his illness and the incidents of his life in hospital are the papers of Leroy (1926), Doiteau & Leroy (1939) and Doiteau (1940); they visited Provence and met Dr Rey and other persons who had known him. Kraus (1941) has contributed a comprehensive review of the medical literature and Gastaut (1956) the latest evaluation of his illness.

Dr Hemphill showed a number of paintings to illustrate this lecture all of which are reproduced in black and white or in colour in the following works: Tralbaut (1959); Cooper (1955); the Phaidon Press publication on Van Gogh (1956); Faille (1939), the complete catalogue of all Van Gogh's known works up to 1939. Black and white reproductions of all the self-portraits are to be found in the catalogue of Van Gogh Self Portraits, Marlborough Fine Arts (1960). The letters of Van Gogh to his brother Théo and to Emile Bernard, and the journal of Paul Gauguin, complete or abbreviated, have been published in several languages.

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Section of Pædiatrics

President B E Schlesinger OBE FRCP

Meeting April 28 1961

Perinatal Mortality Survey under the Auspices of the National Birthday Trust Fund[1]

[Preliminary Communication]

Dr Neville Butler (*London*)[2]

Organization and Returns

A British Perinatal Mortality Survey was made in 1958 under the auspices of the National Birthday Trust Fund; the data are still undergoing analysis but it is possible to give a few preliminary results.

Comprehensive information on the mother and the course and outcome of pregnancy and labour was gathered on all stillbirths and neonatal deaths occurring in March, April and May 1958; as a control population, similar data were gathered on every birth occurring during one week in March 1958. Midwives recorded the data on a questionnaire, aided by hospital medical staff, medical officers of health and general practitioners. Clinical questionnaires were received on 7,927 stillbirths and neonatal deaths in three months, and on 17,077 total births in one week. These returns represented 98% and 95% respectively of the estimated notifications in England, Scotland and Wales. In addition necropsies were carried out at special centres on 88% of the stillbirths and neonatal deaths occurring in March 1958.

Preliminary analysis was based on a 1-in-3 sample of one week's births and on the March stillbirths and neonatal deaths. Analysis of the full 25,000 cases will be reported later.

Hyaline Membrane and Massive Pulmonary Hæmorrhage

Hyaline membrane was the major finding in 2 perinatal deaths per 1,000 live births and massive alveolar hæmorrhage in 0·9 per 1,000. Clinicopathological analysis was made of 100 deaths from hyaline membrane and 52 from massive pulmonary hæmorrhage. Males preponderated in each (65%): the incidence of twins was high (22% and 14%). Mechanical complications were commoner preceding hyaline membrane: for example, placenta prævia in 11%, but in pulmonary hæmorrhage nil; Cæsarean section in 27%, but in pulmonary hæmorrhage 16%. Nonmechanical complications predominated in pulmonary hæmorrhage cases, toxæmia in 65% (25% in hyaline membrane) and 'small for dates' – a birth weight of at least 1,000 g less than the average for gestation – in 55% (33% in hyaline membrane), both these differences being significant. Death occurred by forty-eight hours in 93% of cases of hyaline membrane. The onset of symptoms in pulmonary hæmorrhage was usually after the second day, with death usually on the third to fifth days; twitching or convulsions occurred in 50% without any intracranial lesion except œdema; hæmoptysis (40%) was unaccompanied by other hæmorrhages; vitamin K had been given prophylactically in 45%. Sedation had often been very heavy during labour, and placentæ, where examined, were small.

Dr A E Claireaux (*London*)

Major Post-mortem Lesions

2,368 perinatal deaths in March 1958 (i.e. stillbirths and first-week deaths) have been classified according to the major lesion found at postmortem examination. The results are shown in Table 1. Intrauterine anoxia was the commonest major finding among the stillborn fœtuses, being present in 40% of macerated and 57% of fresh stillbirths. Anoxia was also the major lesion in 11% of first-week deaths making an incidence of 34% of all perinatal deaths. Severe congenital malformation accounted for 15·1% of perinatal deaths (14% of stillborn and 18% of first-week deaths). The central nervous, alimentary and

[1] An account of this meeting has already appeared in the *British Medical Journal* (1961) i, 1313. Table I and Fig 1 are reproduced here by courtesy of the Editor.

[2] Director of the Survey.

Table 1
Major anatomical findings in 2,368 perinatal deaths (Stillbirths and first-week deaths)

	No. of cases	*% of all perinatal deaths*	*Approx. incidence per 1,000 live and stillbirths*
Fresh stillbirth with evidence of intrauterine asphyxia	391	16·5	5·5
Congenital malformation	357	15·1	5·0
Macerated stillbirth without anatomical lesion	347	14·7	4·9
Macerated stillbirth with evidence of intrauterine asphyxia	318	13·4	4·5
Intracranial birth trauma	210	8·9	3·0
Resorption atelectasis with hyaline membrane	138	5·8	2·0
First-week death with evidence of intrauterine asphyxia	101	4·3	1·4
Blood group incompatibility	95	4·0	1·37
Pneumonia	95	4·1	1·23
Resorption atelectasis without hyaline membrane	78	3·3	1·1
Massive pulmonary hæmorrhage	63	2·7	0·9
First-week death without anatomical lesion	65	2·7	0·9
Intraventricular hæmorrhage	57	2·4	0·73
Fresh stillbirth without anatomical lesion	17	0·7	0·2
Extrapulmonary infection	7	0·3	0·1
Miscellaneous	29	1·1	0·3
Total	2,368	100	33·13

cardiovascular systems were the most frequently affected. Resorption atelectasis, with or without hyaline membrane formation, was present in 9·1% of perinatal deaths.

Blood group incompatibility, mainly rhesus, was responsible for 4% of the perinatal deaths. Birth trauma (8·9% of perinatal deaths) was rather more frequent than would be nowadays anticipated among hospital confinements but was probably not unduly high over the country as a whole. It was in this field, however, and that of intrapartum asphyxia that improved obstetric care could most quickly yield improved figures for fœtal salvage. Infection was surprisingly low. The majority was pulmonary (4%) and extrapulmonary infection accounted for only 0·3% of the perinatal deaths. Massive pulmonary hæmorrhage was present in 63 (2·7%) of perinatal deaths. 57 cases (2·4%) had intraventricular hæmorrhage. In 2·7% of first week deaths and 0·7% of fresh stillbirths no anatomical lesion was found and a miscellaneous group of 29 cases (1·1%) completed the series.

The infants dying after the first week of life (i.e. 8 to 28 days) were a relatively small group. As would be expected congenital malformation and infection were the chief findings and together accounted for 136 (83·5%) of the cases.

Dr M J R Dawkins (*Oxford*)

Associations of Intrauterine Asphyxia

Intrapartum asphyxia is defined as death caused by asphyxia in labour. It accounted for nearly a third of all stillbirths and 11% of first-week deaths during March 1958. This group, together with birth trauma, seems the most promising field for future reduction in perinatal mortality, because of our present ignorance about antepartum stillbirths and the management and prevention of prematurity. Normal birth produces asphyxia in the newborn baby. Abnormalities of labour accentuate the degree of asphyxia. Abnormalities of pregnancy may increase the baby's susceptibility to the asphyxia of normal labour. This paper is based on an analysis, by scrutiny of the questionnaires and post-mortems in conjunction with Dr Neville Butler, of the pathology and clinical associations of 451 fœtal deaths from intrapartum asphyxia in March 1958. Results are compared with a control population of one-third of all births from March 3–9, 1958.

The distribution and types of mechanical factors which might produce acute asphyxia in labour are shown in Table 1.

Table 1
Mechanical factors which might produce asphyxia

	Stillbirths	*Respiration never established*	*Neonatal deaths*	*All deaths*
Total	280	104	67	451
Accidental hæmorrhage	30·7%	12·5%	10·4%	23·5%
Placenta prævia	6·1%	4·8%	4·5%	5·5%
Prolapsed cord	12·2%	9·6%	Nil	9·9%
Long first stage	12·2%	17·3%	17·5%	14·4%
Long or difficult second stage	5·7%	9·6%	9·0%	7·1%
Trial of labour for disproportion	1·4%	Nil	1·5%	1·1%
Precipitate or unattended delivery	5·7%	5·8%	9·0%	6·2%
Mature breech delivery	4·4%	12·5%	3·0%	5·9%
Premature breech delivery	10·7%	9·6%	5·9%	9·7%
Shoulder presentation	5·7%	2·9%	Nil	4·2%
Other malpresentations	2·5%	1·9%	Nil	2·0%
Twins	7·8%	2·9%	4·5%	6·2%

The incidence of spontaneous and assisted breech delivery was 15·6% of all cases. The incidence of breech delivery in the control population was 2·8%. Shoulder presentation was present in 4·2% of all cases. Other malpresentations were brow, face and compound. In 6·2% of cases the baby was one of twins. Death of the second twin was three times commoner than death of the first twin.

Table 2 shows the incidence of various nonmechanical factors which may be of importance.

Table 2
Nonmechanical factors in 451 fœtal deaths from intrapartum asphyxia

	Stillbirths	*Respiration never established*	*Neonatal deaths*	*All deaths*
Total	280	104	67	451
Postmaturity	26·1%	33·6%	35·8%	29·7%
Toxæmia — Mild	19·3%	19·2%	20·9%	19·5%
Toxæmia — Moderate	4·3%	8·7%	5·9%	5·5%
Toxæmia — Severe	17·1%	15·4%	13·4%	16·1%
Toxæmia and essential hypertension	3·6%	Nil	Nil	2·2%
Essential hypertension	3·9%	2·9%	2·9%	3·5%
Elderly primipara	7·2%	2·9%	8·7%	6·4%
Maternal age over 35	22·8%	20·2%	13·4%	20·8%
Grand multiparity	14·6%	9·5%	11·8%	13·1%

High maternal age and grand multiparity are both significantly more common in mothers of babies dying from intrapartum asphyxia, whereas elderly primiparity (over 30) is not.

Conclusions

The distribution of pathological findings and associated maternal abnormalities in this series of all deaths throughout the country is closely similar to two recent hospital series of intrapartum deaths (Claireaux *et al.* 1960, Dawkins *et al.* 1961), despite the concentration of abnormalities in hospital series. 30% of these deaths were, in fact, of babies whose mothers were admitted to hospital during labour as emergencies.

The significant maternal associations both in this and in the hospital series were a raised blood pressure and prolonged pregnancy. James (1960) has shown that even normal birth produces chemical evidence of asphyxia in the newborn baby. The human fœtus, like most newborn animals, can survive total anoxia for much longer than the adult. Factors responsible for death were found in 90% of the cases examined. Mechanical factors cause death by interfering with the oxygen supply of the fœtus during labour to such an extent that the normal tolerance is exceeded. The nonmechanical factors of a raised blood pressure and prolonged pregnancy probably act by reducing the fœtal reserves which allow it to survive anoxia. Dawes *et al.* (1959) have shown that the length of survival of newborn animals without oxygen is directly related to the amount of glycogen in the heart. Therefore, any factor which reduces fœtal reserves of cardiac glycogen will reduce the ability to survive the asphyxia of normal birth.

It is generally accepted that both prolonged pregnancy and a raised blood pressure reduce the efficiency of the placenta. The fœtus will then be inadequately supplied with oxygen and food. It is significant that more than one-quarter of the stillbirths in this series were underweight for their gestational age and therefore probably undernourished.

Some obvious problems emerge from this analysis even in its present preliminary stage. It is clear that even uncomplicated labour is a greater risk than normal in women with toxæmia and when the fœtus is postmature. In 14% of the cases in this series, the mother had a diastolic blood pressure greater than 90 mm Hg and was delivered after the 287th day of gestation. The overall incidence of a diastolic blood pressure higher than 90 mm Hg in the mothers of babies dying from intrapartum asphyxia was 45% compared with 26% in the control population. The difference is significant. The incidence of severe toxæmia in mothers of babies dying from intrapartum asphyxia was 16·1% compared with 3% in the control population. The combination of prolonged pregnancy, toxæmia and any abnormality of labour seems to be especially hazardous.

Another high-risk group includes the baby which is recognized as small for dates, usually, but not always, in association with maternal toxæmia. In both these groups very careful supervision of labour is indicated, since the ability to survive anoxia is reduced. There is also the problem of resuscitation of severely asphyxiated infants, since there was no response to attempted resuscitation in more than 20% of these cases.

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Mr R G Law (*London*)

Breech Delivery

In this analysis of breech deliveries, cases of multiple pregnancy, internal version, antepartum fœtal death, gross congenital abnormalities and pre-viable fœtuses were excluded. There remained 174 breech deaths to be compared with a control sample of 113 live breech-born babies. The incidence of breech delivery was 2·8%, 11·9% where the infant was under 5½ lb (2,500 g) and 2·1% when over this weight. The perinatal mortality was 10% and was the same in primiparæ as in multiparæ. In infants under 5½ lb (2,500 g) the mortality was 32%. Asphyxia accounted for 70% and trauma 30% of the perinatal deaths. In the smaller infants the proportion of asphyxia to trauma rose steadily as the weight fell. 16% of primiparæ and 40% of multiparæ went into labour at home, and in all cases the domiciliary mortality was higher, particularly in primiparæ with infants over 5½ lb (2,500 g) where it was six times the hospital rate.

Although a consultant or registrar was present at a large proportion of primiparous deliveries, the general practitioner or midwife dealt with almost half the multiparous labours. Deliveries by an unsupervised houseman had almost twice the mortality of those by a consultant or registrar. The method of delivery in primiparæ was: Assisted in 67% (80%)[1]; extraction in 17% (2%); Cæsarean section in 16% (18%). Breech extractions in primiparæ, though few in number, showed an unexpectedly low mortality, 7%, presumably related to the seniority of the operator. In addition to the cases described, a small number of breeches were born spontaneously, unassisted, but all of them died.

The higher domiciliary mortality, despite selection of worse-risk cases for hospital, suggests that the domiciliary delivery of breech presentations should be discouraged. In deliveries in hospital direct supervision by a consultant or registrar is advisable in all cases, and the high risk with multiparous patients with large babies should be borne in mind.

Mr D G Bonham (*London*)

Cæsarean Sections

The incidence of Cæsarean section in March 1958 was 2·6% of all births. The stillbirth plus neonatal death-rate after Cæsarean section was 6·8% compared with 3·4% overall, or 3·2% of the vaginal births. The perinatal mortality rate according to individual indication was: Disproportion, no losses; delay in labour, 2·5%; elective section, 3·5%; fœtal distress, 5%; failed forceps, 5%. Prolapsed cord showed a mortality of 7%, malpresentation 8%, and placenta prævia 9%. The mortality rose steeply to 24% in the presence of diabetes and antepartum hæmorrhage. The most serious group was toxæmia with a mortality of 30%. Ruptured uterus and concealed accidental hæmorrhage led to 100% mortality.

Fig 1 shows the weights of the infants born by section and the degree of immaturity according to the common indications. It illustrates the serious fœtal loss related to early section for toxæmia.

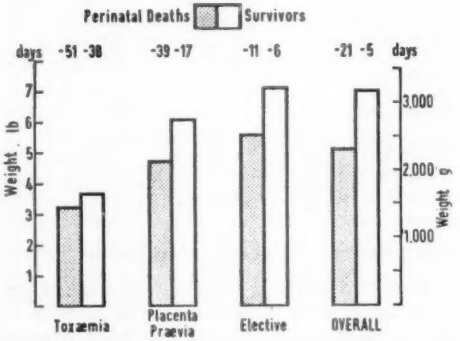

Fig 1 *Mean birth weight and mean days immature, according to certain indications for Cæsarean section, in March 1958*

5% of section deaths were macerated stillbirths, 22% fresh stillbirths, 67% first-week deaths (with 37% on first day) and 6% deaths after one to four weeks. Congenital malformations were responsible for 12% of losses of infants born by section, which was similar to the overall figure of 15%. Perinatal deaths from asphyxia were 25% in those born by section and 21% of all deaths. Atelectasis with or without hyaline membrane occurred in 32% of section deaths, but only in 9% of all deaths.

Interim measures to improve the perinatal mortality rate included hospital booking in more cases with an early confirmation of fœtal maturity and improved antenatal prevention and care of toxæmia. When section was indicated it needed to be done at once in an attempt to reduce the high incidence of fresh stillbirths.

[1]Figures in parentheses relate to multiparæ

Meeting May 26 1961

Hypertension in Childhood
[Abridged]

Professor M L Rosenheim (*London*)

Pædiatricians are fortunate in that, when faced with a patient with raised blood pressure, they do not normally have to consider essential hypertension in the differential diagnosis, but should always be able to find some specific cause. To the best of my knowledge, I have never diagnosed essential hypertension under the age of 16 and only very rarely under 21. The only justification for such a diagnosis is the presence of a marked family history in the absence of any other possible cause for the raised pressure. Unfortunately, while in many children the ætiology of hypertension is obvious, there are still many occasions when the exact cause remains undetermined and this is especially so when full investigation is contra-indicated by the patient's general condition or renal function.

Chronic pyelonephritis forms the commonest basis for juvenile hypertension, and a history of acute urinary infection, of an unexplained pyrexia in infancy or of recurrent abdominal pain may suggest the cause for severe hypertension in adolescence. Anomalies of the urinary tract, whether congenital or acquired, predispose to pyelonephritis. The congenital abnormality may be a simple one, such as a duplex kidney, or may be complex. Chronic pyelonephritis can now be confidently diagnosed by the radiologist and Dr C J Hodson will discuss this. Unilateral pyelonephritis is, of course, not uncommon and is an important curable form of hypertension in childhood. If a diseased kidney is found on one side, it is often difficult to decide whether nephrectomy is indicated. In general, the results of nephrectomy for hypertension are better in younger patients than in adults in whom essential hypertension may be present. Hypertrophy of the opposite kidney is an indication that it is healthy and this can sometimes be confirmed by bilateral renal function tests.

We have been very much impressed, at University College Hospital, by the frequency with which vesico-ureteric reflux can be demonstrated in both children and adults with chronic pyelonephritis, and believe that such reflux may be of ætiological significance (Hodson & Edwards 1960). It has long been recognized that reflux occurs in patients with lower urinary tract obstruction or with neurogenic bladder disturbance but, as Dr David Edwards will describe, vesico-ureteric reflux may occur in the absence of any residual urine or of bladder trabeculation. It is probable that some degree of obstruction to the bladder outflow tract is always present and Mr Innes Williams will discuss present views on the treatment. While reflux is often present in children with a history of recurrent urinary infection, we have seen many patients who, with no history of any attack of acute pyelonephritis, present with either hypertension, albuminuria or renal failure and who, on investigation, have been found to have chronic pyelonephritis with vesico-ureteric reflux.

Chronic nephritis following an attack of acute glomerulonephritis, the nephrotic syndrome or the nephritis of Henoch-Schönlein purpura, is usually accompanied by hypertension and presents little difficulty in diagnosis. Such disease is bilateral and, unless the patient has an identical twin (and one should always enquire!), no dramatic treatment is possible. It is, however, most important to treat such renal hypertension early and to keep it under control, for a rapidly rising or persistently raised pressure produces further renal damage and initiates the vicious cycle that terminates in malignant hypertension and uræmia.

Vascular disease: A variety of diseases of the blood vessels may provoke hypertension in childhood. The presence of coarctation of the aorta must, of course, never be missed, for surgical treatment will often relieve the associated hypertension. A form of aortitis in Bantu children has recently been described from South Africa (Isaacson *et al.* 1959) and a similar condition has been seen in Nigeria (Cockshott 1961, personal communication). This form of aortitis is often associated with severe and fatal hypertension, presumably renal in origin. Such a condition must be extremely rare in this country, but disease of the aorta does occur. I have seen an irregular and calcified aorta in a young girl with a high blood pressure, and medial necrosis of the aorta occurs in Marfan's syndrome. This syndrome is sometimes accompanied by congenital renal abnormalities (Loughridge 1959) and either these or the aortic lesions may provoke hypertension.

The introduction of aortography has revealed the importance of localized anomalies or disease of the renal arteries. Many cases of hypertension due to unilateral or bilateral stenosis of the renal arteries or to aneurysms have been reported, and a considerable number of children have been cured either by local vascular surgery or by nephrectomy. The presence of a bruit over the abdominal aorta or over one of the renal arteries has become an important physical sign.

Polyarteritis nodosa may occur in childhood and the widespread renal vascular lesions may produce severe hypertension. There is one other generalized disease of the arteries in which I have seen severe hypertension. This is the condition of pseudo-xanthoma elasticum and the diagnosis can be made by recognition of the characteristic skin lesion and fundal changes. This condition has been well described recently by McKusick (1960).

Endocrine causes of hypertension are well known in adults, but it is important to remember that they may occur in childhood. In 1957 Cone *et al.* were able to collect 34 cases of phæochromocytoma in children under the age of 14, and, in any child with severe unexplained hypertension, the urine must be investigated for the presence of excess pressor amines or their breakdown products such as 3-methoxy-4-hydroxy mandelic acid. Phæochromocytomata are occasionally familial (Kelsall & Ross 1955, Cone *et al.* 1957) and may be associated with neurofibromatosis.

Another cause of hypertension in childhood, associated with an excess of dopamine, noradrenaline and their metabolites in the urine, is the ganglioneuroma, which is often accompanied by severe diarrhœa. An excellent example of this rare condition, cured by surgery, was recently demonstrated to this Section (Smellie & Sandler 1961).

Abnormalities of the adrenal cortex may also produce hypertension and both Cushing's syndrome and Conn's syndrome (hyperaldosteronism) may occur in childhood. Ross (1959) has recently reported a boy aged 13 with severe hypertension and hypokalæmic alkalosis in whom aldosterone production and excretion were actually low and abnormal steroids, as yet unidentified, were constantly present in the urine. The urinary steroids thus require careful analysis in any child with unexplained high blood pressure.

There are, of course, many other causes for hypertension. Renal tumours may be accompanied by a rise in blood pressure, as may trauma to the kidney, and a perirenal hæmatoma may lead to hypertension in hæmophilia.

Unfortunately relatively few children with hypertension can be cured, but cases of coarctation of the aorta, unilateral pyelonephritis, renal artery stenosis and adrenal tumours are common enough for the possibility of surgery always to be considered, and this is the justification for the complete investigation which is often trying for the patient and the parents. Even if radical cure is impossible, much can now be achieved by medical treatment and the blood pressure can often be adequately controlled by drugs with little inconvenience to the child. Guanethidine appears to be the most effective agent at present available, but mecamylamine and pempidine are also good. Their action can be enhanced and the dose reduced by the associated use of one of the newer thiazide diuretics. As has already been emphasized, treatment should be started early in children with renal hypertension.

It is difficult to say how far the adequate treatment of acute pyelonephritis and the prophylactic use of antibiotics will prevent the occurrence of chronic pyelonephritis and hypertension, but such treatment should be energetically applied. We also do not yet know whether correction of bladder neck obstruction and the relief of vesicoureteric reflux will slow the progress of pyelonephritis once it is established.

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Dr C J Hodson (*London*)

Radiological Changes in the Kidney

It is difficult to obtain a clear picture of the incidence of severe high blood pressure among children. Our own experience of cases encountered at University College Hospital is that, even excluding acute and chronic glomerulonephritis, the majority of cases are of renal origin. The incidence is in fact similar to that among young adults, and the two causative renal conditions are the same, namely chronic pyelonephritis and renal ischæmic disease.

In many cases of hypertension, in young adults particularly, where the causative lesion is pyelonephritis the history dates back to childhood. And though our follow-up statistics are as yet small, we have the impression that pyelonephritic changes in a child's kidney may often be present for some years before severe hypertension supervenes.

Any degree of hypertension in a child which is not explicable on some other basis such as co-arctation of the aorta, glomerulonephritis or phæochromocytoma, is an indication for a thorough radiological examination of the kidneys. In a series of 14 cases that we have collected the ætiological condition has been pyelonephritis in 9, ischæmic renal disease in 4, and 1 was due to a phæochromocytoma. I shall confine my remarks to the radiological diagnosis of pyelonephritis and ischæmic renal disease in children.

Chronic Pyelonephritis

The radiological sign of chronic pyelonephritis is a localized narrowing of the renal substance in one or more places, associated with clubbing of the adjacent calyx if the lesion is large enough (Hodson & Edwards 1960). If unilateral, the affected kidney is decreased in size and there is usually demonstrable hypertrophy on the opposite side. Films taken at short intervals (2 min) at the commencement of pyelography show a diminished output of urine on the affected side, without evidence of impaired concentration. In the vast majority of cases micturating cystography will show that vesico-ureteric reflux is present on this side, and follow-up examinations will show very little growth where the disease is present, growth taking place mainly in the opposite, hypertrophied kidney. Increased distensibility of the affected ureter, or actual dilatation, may be demonstrable; the bladder often shows no abnormality.

In well-established bilateral cases both kidneys tend to be smaller than average, usually one being more so than the other; some growth occurs on both sides, but lags behind the normal. There may be evidence of bladder outflow tract obstruction, such as bladder-neck obstruction, or urethral abnormalities. In a small group of cases pyelonephritic changes have been seen to develop in what were originally apparently normal kidneys, and in all of them vesico-ureteric reflux preceded the typical coarse scarring of chronic pyelonephritis. It may therefore be that the first radiological indication of chronic pyelonephritis is the demonstration of vesico-ureteric reflux in an otherwise normal urinary tract in an infant. At a later stage the typical localized narrowing of the renal substance may be expected to develop.

In a minority of cases recurrent urinary infections may occur in the absence either of vesico-ureteric reflux or of demonstrable localized renal scarring. Whether these cases later develop scarring or reflux, or whether they proceed to some other type of renal lesion, we do not yet know.

Case 1 Female aged 7½ years. Previously healthy except for headaches on and off for a year. Admitted to hospital because of hæmaturia which lasted one week and was not accompanied by fever. On examination she was found to have malignant hypertension, blood pressure 220/150, with albumin and blood cells in the urine. Her blood urea was normal. On only one occasion was an organism cultured from the urine.

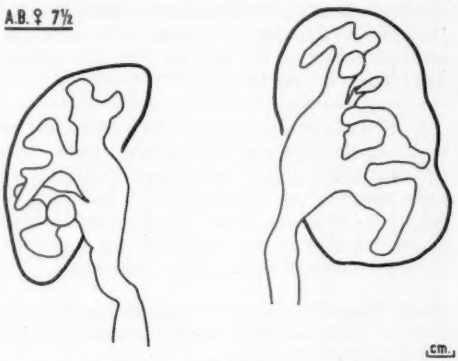

Fig 1 *Tracings of the fifteen-minute I.V.P. film of a child with advanced chronic bilateral pyelonephritis, vesico-ureteric reflux and malignant hypertension*

Intravenous pyelography (I.V.P.) showed the right kidney to be smaller than the left (Fig 1). Both showed irregular 'clubbing' of the calyces, and in many regions there was diminution of the thickness of the renal substance. The ureters were dilated and there was a small residue after micturition. Bilateral chronic pyelonephritis was diagnosed, and micturating cystography showed severe bilateral vesico-ureteric reflux with no demonstrable bladder outflow tract obstruction. A right nephro-ureterectomy confirmed these findings on the right side. Subsequently the blood pressure became controllable by means of drugs.

This case is a very good example of advanced bilateral chronic pyelonephritis with vesico-ureteric reflux complicated by severe hypertension in an apparently healthy child.

Ischæmic Renal Disease

The radiological sign of renal ischæmia is a simple decrease in size of the kidney, or part of the kidney, with preservation of its normal architecture. Thus if the renal artery itself is stenosed the whole kidney undergoes some degree of atrophy. Its outline remains regular and its pelvicalycine structures are in no way distorted. If a branch of the renal artery is involved only the part it supplies will undergo shrinkage and will appear smaller than the rest of the organ. There may be a demonstrable step in the outline where normal and diseased portions join. The opposite kidney, in unilateral cases, may show hyper-

trophy and this enhances the difference in size between the two organs. In bilateral cases both kidneys will be smaller than average though some degree of inequality is usual.

If renal function is measured by means of two-minute films during the early stages of pyelography, it will be seen that less urine is formed in a given period on the affected side, and unless severe preliminary dehydration has been observed the urine on this side will appear to be more concentrated than on the healthy side. The ureters and bladder are normal.

In all 4 of our cases of hypertension associated with renal ischæmia in children, there were demonstrable stenoses in the renal arteries. In 2 cases the stenoses were unilateral, and in 2 bilateral. In the latter there were stenoses in other major branches of the aorta. The diagnosis was made by means of aortography in each case.

Case 2 Female 9½ years. First attended hospital because of slight persistent malar flush. Hypertension was discovered (150/100).

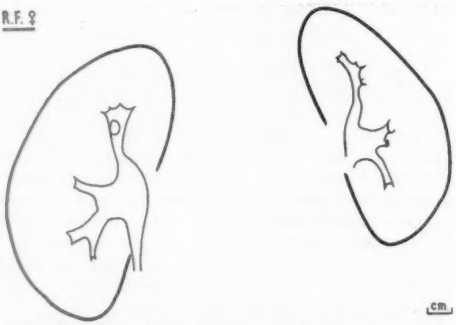

Fig 2 *Tracings of the three-minute I.V.P. film of a child with ischæmic disease of the left kidney due to stenosis of the renal artery*

I.V.P. (*see* Fig 2) showed the left kidney to be smaller than the right with normal pelvicalycine structure and a slightly better concentration of opaque medium. She was considered to have congenital heart disease, and possibly pyelonephritis.

Five years later a second I.V.P. showed both kidneys to have grown slightly, the right more than the left. The left kidney was still the smaller and it excreted a diminished amount of more concentrated urine than the right. This was considered to indicate renal ischæmia and an aortogram was performed. A marked narrowing of the left renal artery at its origin, with post-stenotic dilatation, was noted and a systolic murmur was subsequently heard over the upper abdomen anteriorly.

An attempt to excise the stenosis was not followed by a drop in blood pressure. Subsequent nephrectomy resulted in a fall of pressure to 140/70 mm Hg.

This case well exemplifies the findings in ischæmic renal arterial disease.

In both diseases the affected kidney is therefore reduced in size. In the one there is evidence of focal scarring, in the other there is simple atrophy. In most normal children, except when a marked anatomical difference between the kidneys is present as for example when one is a duplex kidney, there is a remarkable symmetry in size and shape in the two kidneys. This axiom facilitates the recognition of disease in unilateral cases, and one of the main objects of pyelography is so to prepare the child's abdomen that the renal outlines are visible. This is notoriously difficult, particularly in bed-patients, but it can be achieved in most cases by careful preparation beforehand.

Our experience in this realm of urinary disease as a result has been most rewarding, and accurate diagnosis has been possible in many previous doubtful cases.

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Dr David Edwards (*London*)

The Lower Urinary Tract

Examination of the lower urinary tract by cystourethrography has become a routine investigation in all cases of chronic pyelonephritis at University College Hospital. Some of the results have already been published (Hodson & Edwards 1960, Edwards 1960). Fifty-five patients with radiological signs of chronic pyelonephritis have been examined and vesico-ureteral reflux has been demonstrated in 42 (76%).

Vesico-ureteral reflux does not occur in the normal child, but may be produced by a number of pathological conditions (Table 1). Patients

Table 1
Vesico-ureteral reflux

(1) Congenital anomalies of the ureteric orifice
(2) Cystitis – acute, chronic, chemical and following irradiation of pelvis
(3) Neurogenic defect, congenital or acquired
(4) Surgical operations on the ureteric orifice
(5) The megaureter
(6) Lower urinary tract obstruction
(7) Unexplained and associated with chronic pyelonephritis

with chronic pyelonephritis and vesico-ureteral reflux have presented with a great variety of symptoms, which may be associated with a number of renal diseases, but here we are concerned only with 9 patients in the younger age groups who were found to be hypertensive.

The presence of reflux was strongly suspected on the intravenous pyelogram (I.V.P.). The three

main radiological signs which we came to recognize as indicating the presence of reflux are as follows:

(1) *The presence of unexplained vesical residue:* When reflux occurs the bladder empties itself both into the urethra and also into the ureters. After a short time the ureters empty all or part of their contents back into the bladder giving a false and frequently misleading vesical residue. This false residue is a measure of the volume of reflux into the upper urinary tract and is not necessarily an indication of inability of the bladder to empty itself.

(2) *Unexplained dilatation of the upper urinary tract:* Either unilateral or bilateral dilatation may be produced by reflux. Ureteral dilatation may be confined to the lower ureter, may involve its whole length or may be completely absent, as in 5 of our 9 cases. Ureteral dilatation may only be recognized if the ureters are adequately compressed during the I.V.P. or it may only be present during, or immediately after, micturition, and in these cases will only be recognized on the I.V.P. if a film is taken either during, or immediately after, micturition.

(3) *Signs of chronic pyelonephritis:* These have already been discussed by Dr Hodson.

Demonstration of Vesico-ureteral Reflux

Reflux from the bladder into the ureters may occur at rest or only during micturition. It is always greatest during micturition. It therefore follows that films must be obtained during micturition as well as at rest, and it is, of course, of great importance to demonstrate normal bladder contraction. The bladder neck and urethra must be seen in order to attempt to exclude the presence of obstruction at, or below, the bladder neck.

The density of the bladder shadow following intravenous injection of contrast medium is rarely sufficient to demonstrate detail at the level of the bladder neck and the urethra; contrast medium in the ureters which has been excreted by the kidneys leads to confusion and may be mistaken for reflux from the bladder. It is regrettable that catheterization of the bladder seems inevitable. Following catheterization a note is made of any bladder residue and the bladder filled to full capacity with contrast medium. Films of the bladder, urethra, and ureters, either ciné or stills, are taken at rest and also during micturition. It is essential that the bladder neck and urethra are well demonstrated and for this purpose the patient must be rotated into the oblique position.

Reflux is easily demonstrated but bladder-neck obstruction may be extremely difficult, and indeed quite impossible to exclude radiologically. The classical case of bladder-neck obstruction with a true vesical residue, bladder trabeculation and/or diverticula, and a collar-like impression on the bladder neck, is easily recognized. However, these signs may be absent and it is probably wise in the presence of reflux to assume that bladder-neck obstruction may be present even if there are no radiological signs of its presence.

Nine young patients with chronic pyelonephritis and hypertension have been examined. They all showed vesico-ureteral reflux, and their particulars are briefly summarized in Table 2. There was evidence of urinary infection in 5 patients and bladder-neck obstruction was demonstrated in 3. The cause of the vesico-ureteral reflux remains obscure in 6 of these patients. On cystoscopy the bladder mucosa was normal, the ureteric orifices were normal in appearance, and there was no clinical or radiological evidence of bladder-neck obstruction.

Table 2
Hypertension, chronic pyelonephritis and reflux

Initials	*Age on presentation (years)*	*Sex*	*Evidence of infection*	*Ureteral dilatation*	*Lower urinary tract obstruction*	*Blood pressure (mmHg)*
(R W)	19	F	Yes	No	No	190/120
(P B)	17	M	No	Yes	Yes	140/100
(B J)	14	F	No	No	No	240/160
(V W)	13	F	Yes	Yes	Yes	210/120
(F L)	12	F	No	Yes	No	150/100
(L S)	14	F	Yes	No	Yes	210/140
(J S)	11	F	No	No	No	210/120
(M U)	10	F	Yes	No	No	150/105
(A B)	9	F	Yes	Yes	No	220/170

We have now had the opportunity of following two patients in whom the date of onset of reflux could be accurately determined. In one patient reflux was produced by surgical intervention at the lower end of the ureter, in the other it followed a chemical cystitis produced by the injection of phenol into the bladder. Both patients subsequently developed radiological changes identical with chronic pyelonephritis. Histological examination of a kidney removed from one of the two patients confirmed the presence of chronic pyelonephritis. Some of our patients with chronic pyelonephritis and reflux have been followed for some years and have shown a gradual progression of the renal disease. There seems to be little doubt that reflux, once established, produces progressive destruction of renal tissue and we believe that cysto-urethrography is indicated in all cases of chronic pyelonephritis.

Case Reports

Case 1 L S, female aged 14 years, presented with a history of headaches on first waking in the morning for two years, and recent blurring of vision. Blood pressure 210/140; fundi showed Grade I changes. Blood urea 15 mg%; urine contained a few pus cells.

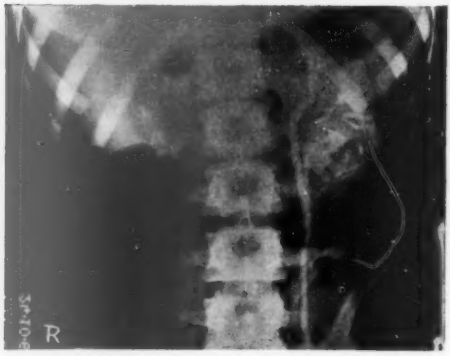


Fig 1 *Bilateral chronic pyelonephritis. Changes on left side confined to lower half of duplex kidney*

I.V.P. demonstrated the radiological changes of chronic pyelonephritis on the right side, and a duplex left kidney, with a double ureter. The upper half of the duplex kidney was normally hypertrophied but the lower half showed the changes of chronic pyelonephritis (Fig 1). There was no ureteral dilatation. The cysto-urethrogram demonstrated a normal bladder with reflux on the right side filling the pelvicalycine system. On the left side reflux only occurred into the ureter draining the diseased lower half of the left kidney. There was a distinct collar-like impression at the bladder neck indicating the presence of bladder-neck hypertrophy. The urethra was normal. Cystoscopic examination demonstrated the presence of two ureteric orifices on the left side and a prominent posterior lip at the bladder neck.

Case 2 F L, female aged 12 years, had a history of headaches for four months. No urinary symptoms. Blood pressure 150/100; fundi normal. Blood urea 30 mg%; urine normal, no albuminuria, sterile on culture. I.V.P. demonstrated the presence of left-sided chronic pyelonephritis and slight dilatation of both ureters, the right kidney was hypertrophied and showed no evidence of disease (Fig 2). Bilateral reflux occurred on cysto-urethrography (Fig 3). Cystoscopy showed no abnormality.

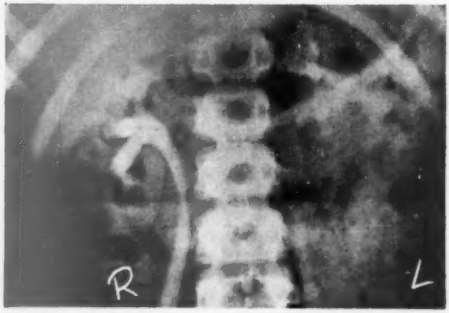
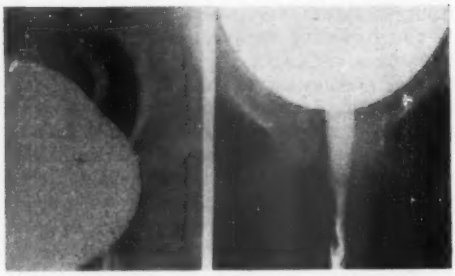


Fig 2 *Unilateral chronic pyelonephritis*



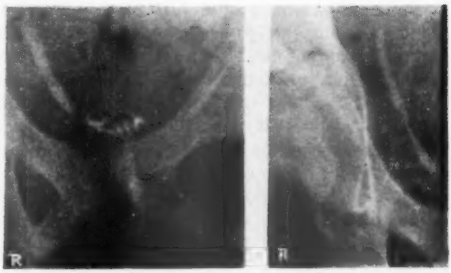


Fig 3 *Cysto-urethrogram with bilateral reflux*

A plastic repair operation was carried out on the lower end of the right ureter combined with an advancement flap operation on the bladder-neck. The post-operative cysto-urethrogram showed that reflux persisted on the left side but did not occur on the right side. The left kidney was subsequently removed and histological examination confirmed the presence of chronic pyelonephritis.

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Mr D Innes Williams (*London*)

Surgical Aspects[1]

The differential diagnosis between hypertension due to pyelonephritis and renal artery stenosis may be difficult, and in reviewing old cases it is essential to reassess the criteria originally used in diagnosis. A case recently demonstrated by aortography to have a narrow renal artery was originally

[1]A summary of the author's experience of hypertension due to phæochromocytoma, neuroblastoma, nephroblastoma and Cushing's syndrome is omitted due to lack of space.

investigated in 1954, and was then regarded as pyelonephritis. Since then, not only have our radiological methods improved but the pathologists have altered their views upon histological diagnosis. Besides this case, there have been two other children who had nephrectomies for what were then regarded as small pyelonephritic kidneys, but who have definite ischæmic lesions on review:

Case 1 Boy aged 4, with severe hypertension (210/135), investigated over a period of one year in 1950 before a decision was made to remove the smaller, but functionally normal, left kidney. After nephrectomy the blood pressure fell rapidly to 100/60 and has remained down for ten years. This specimen is, to all intents and purposes, a histologically normal kidney.

Case 2 Girl aged 8 years, with one year's history of headaches, frequency and loss of weight and a blood pressure of 200/160, with a normal blood urea and bilateral papillœdema. Nephrectomy made no difference to her blood pressure, she died one week after her operation with perforations in the intestine and necrotizing arterial lesions in many organs. Her kidney is now reported as showing ischæmic changes.

Dr Hodson has already described the methods of diagnosis and has emphasized the importance of the finding of a small kidney without irregularities or calyceal abnormality. Recorded cases of renal artery stenosis in children, have, I believe, all had small kidneys, but there is some danger that we shall miss stenoses of branches of the renal artery producing very little alteration in size. Differential renal function studies, paying particular attention to the excretion of water and sodium, are regarded as vital by many urologists, but our own success has been limited, partly by technical factors. It has been impossible to pass large ureteric catheters required for complete collection of urine through the small cystoscopes which the child's urethra will admit.

Pyelonephritis is undoubtedly the commoner cause of hypertension. I have records of 22 cases with adequate investigations under the age of 15. This must represent a very small proportion of all cases of pyelonephritis, but one cannot tell whether a number of affected children will develop hypertension in later life. In 11 of the 22 cases hypertension only appeared when there was advanced bilateral renal destruction and a very high blood urea. Two of them, at the age of 11 months and 3 years, had two small kidneys, and the possibility that pyelonephritis complicated renal artery stenosis cannot be eliminated; 3 had very long-standing obstruction, due to neuropathic bladder, bladder-neck obstruction and urethral valves; they developed hypertension late in childhood. Probably if our records of terminal uræmias were more complete, there would be many more with hypertension. The remainder with a high blood urea had a bilateral pyelonephritis or pyelonephritis of a solitary kidney of the type which used to be called primary, but is now known to be associated with ureteric reflux.

In the other 11 cases hypertension was present without renal failure, but in only 3 was the lesion judged to be unilateral. One had a hydronephrosis due to pelvi-ureteric obstruction with infected urine, the blood pressure was unaffected by pyeloplasty, but was brought down by nephrectomy. Another was judged to be unilateral by aortography, which showed an apparently normal kidney on the opposite side; removal of the contracted kidney caused no fall in pressure, however. One bilateral case was amenable to surgery.

Case 3 Girl aged 2 years, with cardiac failure and a blood pressure of 160/100, had a double right kidney with the ureter from the upper pole ending in the vagina, grossly infected, while a single ureter on the left, also infected, ended in the urethra. A right hemi-nephrectomy and a left total nephrectomy was therefore undertaken, at first with little effect. But over the course of three months the pressure fell to normal, and now, six years later, it is 130/60. She has not received hypotensive drugs.

In the remainder, the pyelonephritis was evidently bilateral, although in 3 it was so asymmetrical as to provoke us to undertake nephrectomy of the grossly contracted kidney; always without benefit. In several of these, however, the child has remained extraordinarily well on medical treatment and at least one survives seven years after operation without any sign of deterioration, although her blood pressure is still raised.

These findings accord well with those recorded in the literature, and certain generalizations seem justifiable: (1) when hypertension complicates pyelonephritis it is due to a parenchymal lesion which is irreversible; it can be eliminated only by surgical excision. (2) Pyelonephritis is normally bilateral, although often asymmetrical, and if progressive leads to renal failure. In children it is usually associated with vesico-ureteric reflux or other ureteric anomaly, but only on rare occasions is such an anomaly unilateral. (3) The first question to be asked in pyelonephritic hypertension is: Can the diseased kidney, or part of the kidney, be excised, and leave an adequate amount of entirely normal kidney behind? If we adopt the very strictest criteria for normality of the other kidney, the answer will very seldom be affirmative and radical surgery is therefore rarely advisable in pyelonephritis. (4) If the disease is not eradicable, then everything possible must be done to preserve renal function, for the prognosis of hypertension varies considerably according to the blood urea

level. Occasionally the prevention of infection will involve the removal of an infected non-functioning kidney, but it should not be supposed that this will have an influence on the blood pressure in bilateral disease. Bladder-neck obstruction must unquestionably be treated, but there is still room for argument about the operative treatment of reflux. If it is believed that reflux affects the kidney only by predisposing it to infection, then operation is indicated if infections recur, but perhaps not if the urine remains consistently sterile.

Clearly hypertension complicating pyelonephritis has a poor prognosis compared with renal artery disease: we cannot often cure it, but we can, perhaps, do something to prevent it. Almost all cases of chronic pyelonephritis in childhood have had recurrent urinary infections, and this problem of hypertension emphasizes the need to investigate and treat recurrent pyuria before radiologically demonstrable pyelonephritic scarring has occurred. Many of the urinary tract anomalies predisposing to this recurrent pyuria have been known for a long time, but it is only comparatively recently that we have realized the importance of bladder-neck obstruction and ureteric reflux in girls.

We have reviewed 500 cystograms in children and are in no doubt that reflux, in the presence of severe lower urinary obstruction, favours rapid development of hydronephrosis, but where the obstruction is mild, or absent, reflux favours pyelonephritic contraction with recurrent infection. Reflux is, however, often present before radiologically perceptible renal changes, and treatment at this stage seems to offer a chance of preventing deterioration. Reflux-preventing operations aim essentially at lengthening the intramural segment of the ureter to restore valvular action. Many methods are available, varying somewhat in their technical success rate. I have performed such operations on 53 children and we are preparing a survey of the early results – they look encouraging in terms of prevention of recurrent infections, but clearly the final answer in terms of prevention of pyelonephritic contraction must be delayed for several years.

As an interesting variant on renal hypertension, mention may be made of two cases of hæmophilia with well-marked hypertension. One of these, aged 10 months, was admitted under the care of Sir Wilfred Sheldon, with a large perinephric mass, presumably a hæmatoma, and a massive hæmaturia with clot retention. After prolonged treatment the bleeding was controlled. No pyelographic abnormality could be demonstrated and the hypertension remained severe, although the hæmatoma subsided. The child succumbed not long afterwards. A second patient had a history of hæmatoma in the loin two years before admission under the care of Dr G H Newns for investigation of hypertension, but no abnormality could be detected radiologically. One imagines that both these cases had their kidneys compressed from outside, as in the original cellophane wrapper experiments of Page (1939). In children without hæmophilia this would certainly have justified exploration.

Hypertension is a complication of many, but not all, cases of polycystic disease, usually those with a high blood urea.

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Section of Orthopædics

President A L Eyre-Brook MS

Meeting May 13 1961
at the Royal Infirmary Sheffield

Short Papers [*Abridged*]

A Dye Technique for the Assessment of Viability of the Femoral Head

by E R Price MB MRCP FRCS (*Barnsley*)

The technique described is an attempt to measure the blood flow through the femoral head at operation for internal fixation of subcapital and transcervical fractures of the femoral neck.

It is a dye clearance technique: a measured amount of dye (Coomassie blue, I.C.I.), in practice 5 c.c of 4% solution, is put into the femoral head at operation by means of a special needle, the concentration in the plasma is determined by taking serial venous blood samples, heparinized or clotted, from an arm vein at one, two and five minutes, and the dye evaluated chemically. It can also be measured by a colorimetric method or an oximeter can be used on the patient.

So far the method has been used for prognosis, and the results are only now becoming assessable in the light of subsequent progress. The longest follow-up is twenty-three months.

In the 21 patients who have been included in this series, the results have fallen into three categories:

(1) Dye absent from plasma – 7 patients. All developed avascular necrosis.

(2) Dye concentration less than 2 mg% in 1–5 minute specimens of plasma – 4 patients. Three developed avascular necrosis. One settled but united.

(3) Dye concentration over 2 mg% in 1–5 minute specimens of plasma – 10 patients. Nine united (one with patchy necrosis). One head collapsed.

If the apparent correlation between absorption of Coomassie blue from the femoral head and subsequent viability of the head is confirmed in a larger series, the technique, already simple, could be modified for use in the operating theatre by centrifuging the 2-minute heparinized specimen of blood and comparing the plasma with a standard containing 2 mg% of Coomassie blue. If the sample is bluer than the standard, then viability can be assumed and Smith-Petersen pinning performed. If the sample is less blue than the standard, clinical judgment must be used to decide on the procedure to be performed. If the sample contains no dye some primary procedure other than Smith-Petersen pinning is indicated.

The Fate of Human Decalcified Bone Grafts

by W J W Sharrard MD FRCS and
D H Collins OBE FRCP (*Sheffield*)

Recent experimental work by Ray & Holloway (1957) on the bridging of bone defects in rats indicated the superiority of decalcified bone implants over whole bone and deproteinized grafts. There seems to be no record of the use of decalcified bone grafts in man since the latter part of the nineteenth century.

The opportunity for controlled observations on the implantation of different bone preparations presented itself when three scoliotic children, aged 10 to 12 years, entered hospital for spinal fusion necessitating multiple-stage operations. In the course of these operations, grafts of bone-bank rib and of autogenous cancellous bone from the ilium were implanted alongside the vertebral spines; each patient received a decalcified graft and at least one graft of untreated bone. Biopsy of each graft site was made six weeks after implantation, and the biopsy tissues were examined histologically after various staining procedures.

The results, in short, showed that decalcified autogenous bone was perfectly acceptable to the tissues and formed a good scaffold for the appositional growth of new reparative bony callus. The long-term results were satisfactory, and X-ray examination revealed an excellent degree of calcification of the repair tissue at the site of the decalcified grafts.

Decalcification of the bone graft pieces was effected by ethylene-diamine tetra-acetic acid (E.D.T.A.), and all manipulations were sub-

jected to the most rigorous bacteriological control since preliminary tests proved that this chelating agent is bacteriostatic but not bactericidal.

A more detailed, illustrated account will be published later.

REFERENCE
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A Study of Perthes' Disease Preliminary Report

by E G Herzog MB (*Sheffield*)

During the last two years I have conducted an investigation into Perthes' disease at King Edward VII Orthopædic Hospital, Sheffield. I have so far collected and analysed 133 cases from my own and other hospitals in the region.

The age incidence has been, as in other series, between 3 and 10 years, with a peak incidence at 5. Males to females were as 4 : 1.

Loss of internal rotation is probably the best early, single physical sign. The pain of onset is often intermittent. It disappears while the child is still running about at home only to return a few weeks later. It disappears very promptly when bed rest is instituted.

I have opened three joints and confirmed what has been reported many times before: that in the early stages a well-rounded cartilaginous head can be found in the presence of a flattened bony nucleus.

I have found no evidence that the flattening in Perthes' disease occurs rapidly as a single catastrophic event like the slipping of an epiphysis. In fact, I have been able to collect the X-rays of 4 patients to show the opposite. These were cases which were missed at their first attendance. In the three, eight, ten and eighteen months which elapsed before they were diagnosed and admitted the femoral head flattened proportionately 1/16, 2/16, 3/16 and 7/16.

I reviewed 20 patients who had completed their treatment from three to eight years previously and were no longer attending the out-patient clinic. They were all free from pain and had good movements, even in the presence of marked flattening. I therefore decided to take the X-ray as a guide to the success or failure of the initial treatment. For the purpose of this paper I assume, therefore, that a well-rounded femoral head, well contained in the acetabulum, constitutes a good result and that flattening leads to osteoarthritis in later life. The degree to which it does so would have to be the subject of a separate investigation. I also assume that the worse the flattening the greater the chances of osteoarthritis supervening.

In order to assess the results of treatment I separated out two groups: (1) Patients treated in hospital by prolonged immobilization. (2) Patients who had a short period in bed and were then treated as out-patients on a patten-ended caliper. The results (Table 1) were better for the patients treated by prolonged bed rest.

Table 1
Results of treatment in Perthes' disease

Total number collected:			133 cases		
Discarded:					
Incomplete records	10	} 26 cases			
? not Perthes' disease	8				
Inconsistently treated	8				
Analysed:					
Frame	73	} 107 cases			
Caliper	34				
Results:					
	Treated on frame			*Treated on caliper*	
	Cases	*%*		*Cases*	*%*
Excellent	7	9·5		1	3
Good	50	68		14	41
Fair	10	14		8	24
Poor	6	8·5		11	32
Total	73	100		34	100

Table 1 shows the results of 133 cases. I discarded 26 because in some the records were incomplete, several were probably not cases of Perthes' disease and in a few no persistent course of treatment was followed.

In assessing the results I compared each patient's last X-ray with his first, so that I gave good marks to a flattened head if it had not flattened further or even excellent if it had expanded. It is little use comparing the number of good results by one form of treatment with the number of good results by another, without relating the end-result to the state of the patient when treatment was started.

Dislocations of the Knee

by David K Evans FRCS (*Sheffield*)

Traumatic dislocation of the knee is rare but becoming commoner. Recently small series of cases have been reported by Southgate (1958) and Kennedy (1959). The unusual postero-lateral subluxation first reported by Clarke in 1942 was fully described by Quinlan & Sharrard in 1958.

This paper reviews 15 further cases.

Classification: The possible directions in which the tibia may displace and the numbers of each in this series are as follows: Anterior 5, posterior 5, lateral 1, medial 0, postero-lateral 4.

The anterior and posterior dislocations usually have an element of medial or lateral displacement. Except for noting a complication associated with

the antero-medial type, no further subdivision is necessary.

Reduction: There is seldom difficulty in reducing anterior, posterior, medial or lateral dislocations by traction and direct pressure under general anæsthesia. The majority of the postero-lateral subluxations require open reduction.

The medial hamstring tendons may lock between the femoral condyles in a lateral dislocation but can be released by flexion of the knee to a right angle (Smillie 1946).

Occasionally in a medial dislocation the lateral capsule is interposed between the lateral condyles. The styloid process of the fibula or even the lateral popliteal nerve may be included in the joint (Platt 1940). Open reduction is necessary.

Duration of immobilization: Ten of the 11 complete dislocations in this series were immobilized for up to twelve weeks. One that remained in plaster for four months remained permanently stiff and painful and was subsequently arthrodesed. Six weeks' immobilization is sufficient.

Complications: (1) *Anterior dislocations:* Two of the 5 in this series suffered a lateral popliteal palsy. Both were antero-medial dislocations – the direction in which the nerve is most stretched.
(2) *Posterior dislocations:* Two of the 5 developed vascular complications. In one the popliteal artery thrombosed and amputation was necessary. In the other the circulation in leg and foot was very poor for a week after the injury, this ischæmia later causing an equino-cavo-varus deformity of the foot with clawing of the toes.

Four of the 5 showed damage to the extensor apparatus (avulsion of the tibial tubercle, or of the lower pole of the patella, or rupture of the patellar tendon).

These observations contradict the statement of Conwell & Alldredge (1937) that damage to the popliteal vessels is commoner in anterior dislocations and is produced by hyperextension.

Postero-lateral subluxations: Two of these were reduced by closed manipulation. This is uncommon as the medial capsule usually tightly button-holes the medial femoral condyle, and open reduction is necessary.

Results: (1) *Range of movement:* Excluding the arthrodesed knee all except two regained at least 120 degrees of flexion. The two exceptions flexed to 90 degrees.
(2) *Stability:* All but 2 were stable and showed only slight symptomless laxity of the collateral and/or cruciate ligaments.
(3) In the absence of fractures, degenerative osteoarthritis was late in developing. It occurred first in the patello-femoral compartment.

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Hæmobursa in Kneeling Miners

by W J W Sharrard MD FRCS (*Sheffield*)

The commonest variety of beat knee that may arise in kneeling miners is an aseptic bursitis of one of the bursæ in front of the knee or upper leg. One, the prepatellar bursa, occurs naturally. Another, the subcutaneous infrapatellar bursa, though described in standard textbooks of anatomy, was not found in 30 consecutive autopsies in non-miners but was present in 21 out of 30 miners undergoing meniscectomy, and must therefore be considered an adventitious bursa.

The condition may present (1) as an acute bursitis in a previously unaffected bursa, (2) as a chronic painless bursitis, or (3) as an acute painful bursitis occurring in a chronically enlarged bursa. An exhaustive study of all possible environmental and personal factors in the incidence of beat knee showed that the only constant factor was kneeling at work. In men who had suffered an acute or acute-on-chronic episode there was sometimes a history of direct trauma to the affected bursa but, in others, the bursa became enlarged and painful during the course of normal work on the knees or even some hours after a shift of work.

In 30 patients who developed acute bursitis in a previously unaffected bursa, only 5 of whom had a history of direct trauma, pure blood was obtained on aspiration in 29 of them. A mixture of blood and pus was aspirated in 1 patient. In those suffering from an acute-on-chronic bursitis, blood-stained bursal fluid was often obtained. The initial pathology of aseptic bursitis in kneeling miners is thus a hæmobursa.

Although the ætiology of the hæmorrhage is clear in patients giving a history of direct trauma, it is not so easily explicable in the others. A mechanism to account for it was revealed in a patient who gave a history of acute painful swelling of the prepatellar bursa several hours after having been kneeling. The bursa was aspirated and contained pure blood. One week later, the

bursa was removed and section of its wall showed that a spontaneous rupture of one of the large vessels lying in the wall of the bursa had occurred.

Experiments were conducted to determine the site and amount of pressure on the knee in working miners. They showed that during the process of shovelling, the maximum site of pressure commenced at the tibial tubercle, moved forward to the lower pole of the patella with the forward stroke of the shovel, and then returned to the tibial tubercle as the coal was discharged. At the moment of discharge of coal from the shovel to a conveyor belt almost all the combined weight of the man, his shovel and the load on the shovel was being taken on one knee, usually the left knee. Direct pressure readings showed that the total load could be as great as 200 lb over an area of knee measuring 1 to 2 square inches. Pressure variations from nil to this level occurred at every stroke of the shovel, that is 15 to 20 times per minute. These experiments suggest that repeated and severe fluctuations in pressure may cause rupture of a vessel in the bursal wall giving rise to acute hæmobursa. Reactionary fibrosis occurring in the bursal wall following the initial attack may give some measure of protection against further hæmorrhages, though hæmorrhage may also be responsible for an acute episode in a chronically enlarged bursa.

The knee pads worn by miners vary considerably in the degree of protection that they offer to these forces. Some, for instance those made of felt and belting, do little other than to protect the skin of the knee from the trauma of coal particles and rough floors. A knee pad that appeared to offer the best protection was the 'Bursa' pad in which the kneeling surface contained a combination of sorbo rubber and rubber spikes allowing a measure of cushioning without undue instability. It was found that this pad, worn by a patient suffering from a recent acute incident, would allow him to return to work when other pads did not do so. In an attempt to estimate the value of the 'Bursa' pad in the prevention of beat knee, pads of this kind were distributed over a period of eighteen months to successive groups of men working at the coal face in one colliery. Unfortunately, difficulties in maintaining a random distribution of the pads rendered the numbers that could be included in the final analysis too small to give a statistically conclusive result.

Acknowledgments: I wish to acknowledge the work done in the course of these investigations by Mr D M Caird and Mr J McKessack who did much of the field work. The research was undertaken through a grant from the Medical Service of the National Coal Board.

Hot-bar Injuries

by J Graham Ross FRCS (*Sheffield*)

The hot-bar injury occurs in steel rolling mills. It is a penetrating injury, usually of the leg, by a red hot steel bar.

Steel is rolled in two main forms, either as sheets or bars of various sizes. In the latter process a billet of steel, approximately 5 ft in length, and 4 in. in cross section, is heated in a furnace, and then passed through graded rollers until it reaches the requisite size. Men stand at either side of the rollers to pick up the steel in long-handled tongs, and guide it into the appropriate roller. As the steel becomes narrower, so it increases in length, and becomes pliable. It is these narrow bars coming out of the rollers at knee level that cause the penetrating injuries (Fig 1).

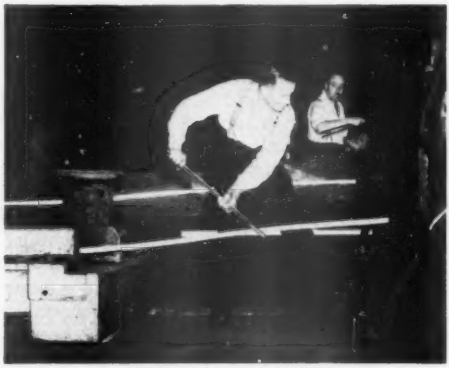

Fig 1 *The narrow bar comes out at knee level and is held in long-handled tongs*

Incidence: During the last ten years, 27 hot-bar injuries have been treated in the Orthopædic Department of the Royal Infirmary, Sheffield; all but 1 have been in the leg. Fourteen patients had skin and muscle lacerations alone; 4 had bone or joint injury; 2 division of main vessels; and 5 damage to major nerves.

Pathology: There are two main features of the wound that have an important bearing on treatment: (1) It is a combination of laceration and burn. (2) Because the bar is red hot, sepsis is rare.

Treatment: The usual principles underlying the treatment of lacerations apply, but it is necessary to excise more widely than for simple lacerations, particularly at the entry wound where the skin is most extensively burnt. The track of the hot bar is

laid open, and all burnt tissue excised. The wound is closed, if necessary using some simple plastic technique, and no drainage is required,

Healing: Primary healing was obtained in 16 cases. Failure of primary healing in the remainder was due to a variety of causes, but particularly to inadequate excision of burnt tissue, and hæmatoma formation in the wounds of the popliteal fossa.

Damage to specific structures: There were 2 cases of fractured femur and 2 where the bar penetrated the knee-joint. All but 1 of these patients had full recovery of function.

The superficial femoral vessels were divided on two occasions. One of the patients was admitted *in extremis* and died shortly afterwards. The other had the vessels ligated, and subsequently required an above-knee amputation.

Five patients had major nerve injuries. The lateral popliteal nerve was most frequently damaged. In 3 cases the lesion was in continuity and full recovery occurred, but in a fourth both medial and lateral popliteal nerves were divided, and primary suture was unsuccessful. The sciatic nerve was completely divided in the upper third of the thigh in the last patient. Primary suture, after wide excision of burnt nerve, was performed, and fourteen months after the injury there is contraction in the calf muscles.

On the whole, recovery from these injuries has been satisfactory, considering the potentialities of a red hot steel bar as an industrial hazard.

A **Demonstration of Cases** was given by the Accident and Orthopædic Department.

Meeting June 17 1961
at the Bristol Royal Infirmary

Short Papers [*Abridged*]

Vertebral Biopsy for Doubtful Neoplasms

by Norman Capener FRCS (*Exeter*)

Mr Capener described the application of his lateral rachotomy approach (Capener 1954) which had originally been devised for the treatment of Potts' paraplegia.

Twenty explorations of such vertebral lesions had been performed, and eight of these were described in detail. These were examples of myeloma; renal pelvic carcinoma; male mammary carcinoma; carcinoma of the cervix uteri; carcinoma of the bronchus; one which proved to be tuberculosis of the 4th lumbar vertebra and two young children with eosinophilic granuloma (Calvé's disease). The latter cases were of particular interest.

Eosinophilic Granuloma

Case 1 A P, boy aged 4
Admitted with acute abdominal symptoms and a history of falling about for two weeks. There was marked spinal rigidity and mid-dorsal tenderness. Radiographs showed a mild compressive lesion of the 7th dorsal vertebral body. In spite of negative tests for tuberculosis, this was at first thought to be the diagnosis.

Case 2 Y B, girl aged 6
While A P was under treatment, Y B was admitted with acute abdominal symptoms and difficulty in standing. There was a small kyphus in the mid-dorsal region with local tenderness and spinal rigidity. Again, tests for tuberculosis were negative. It was decided to explore the 10th dorsal vertebral body which showed partial collapse. Histology showed eosinophilic granuloma tissue.

It was then discovered that both children had lived as next door neighbours until a year previously.

Study of the environment, including the radioactivity of water supplies, produced no significant information.

A P was now dealt with in a similar manner by vertebral exploration, and again eosinophilic granuloma was found. Both patients in the course of the next few months showed the typical appearances of vertebra plana (Calvé).

The operative intervention was quite straightforward, and at no time caused anxiety. These two cases confirmed again the relation of Calvé's disease to eosinophilic granuloma already noted by Fairbank, Pouyanne, Compere and other writers.

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Stapling of the Spine for Scoliosis

by Hedley Hall FRCS (*Bath*)

Nachlas & Borden (1951) showed that by stapling the spines of dogs they could produce a lateral curvature accompanied by vertebral rotation and that by reversing the position of the staples from the concave to the convex side, the curve so induced could be corrected. This procedure they suggested would be useful in the investigation of the properties of spinal curvatures in dogs and hoped that it might also be of value in the treatment of scoliosis in human beings.

It was not the first time that restraining the growth on the convex side of the curve had been suggested as a means of treating scoliosis. As a result of his experimental work, Haas suggested it in 1939, and in 1940–42 LeMesurier attempted unsuccessfully, to cure or control scoliosis in 4 children by damaging the growth plates (LeMesurier 1951).

The idea seemed so attractive and offered such a simple solution to one of the more difficult orthopædic problems that I decided to try the effect of stapling the spines of 5 children with scoliosis.

Case 1 M H, male. Congenital hemivertebra. Two staples. Age 2 years: curve of 30 degrees. Age 3 vears (stapled): curve of 30 degrees. Age 9 years: curve of 32 degrees.

The majority of such cases, however, are not progressive, so the fact that the curve has not increased cannot be claimed as due to the staples. Two things can, however, be learned: (1) The staples can remain *in situ* for six years in an active child without serious extrusion. (2) The staples can be broken: these staples broke four years after insertion.

Case 2 W C, female. Paralytic curve. Three staples. Age 9 years (stapled): curve of 30 degrees (Fig 1A). Age 11 years (spine graft): curve of 65 degrees (Fig 1B). Age 18 years: curve of 65 degrees.

The main increase in this curve occurred above and below the staples which thus did control the curve in their limited area.

Case 3 S M, male. Infantile scoliosis. Five staples. Age 2 years: curve of 47 degrees. Age 6 years (stapled): curve of 60 degrees. Age 9 years: curve of 62 degrees. Age 11 years: curve of 75 degrees.

Here again the bulk of the increase in the curve occurred above the stapled area.

Case 4 V D, female. Idiopathic scoliosis. Eight staples. Age 9 years (stapled): curve of 22 degrees. Age 13 years: curve of 80 degrees.

Here the number of staples was adequate for the curve treated but during the four years of observation the stapled area increased in curvature by 60 degrees.

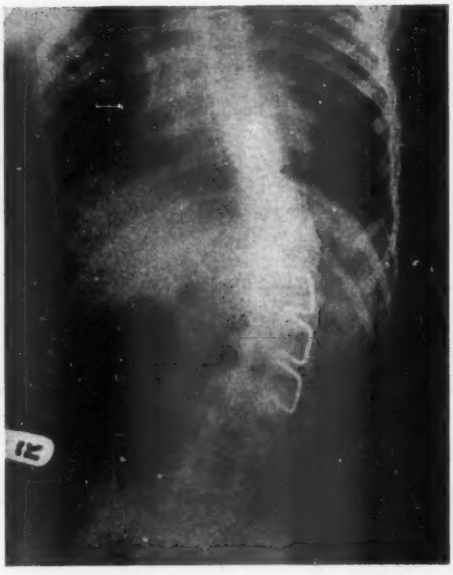

Fig 1A **Case 2** *Aged 9*

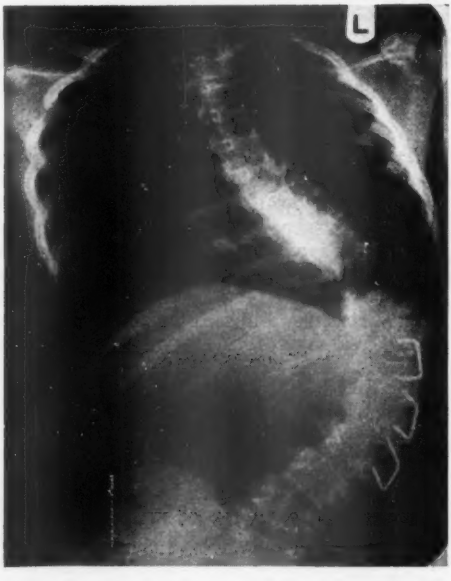

Fig 1B **Case 2** *Aged 11*

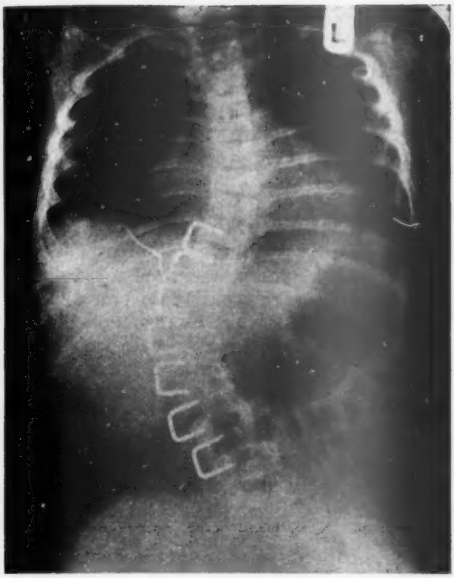

Fig 2A Case 5 *Aged 5*

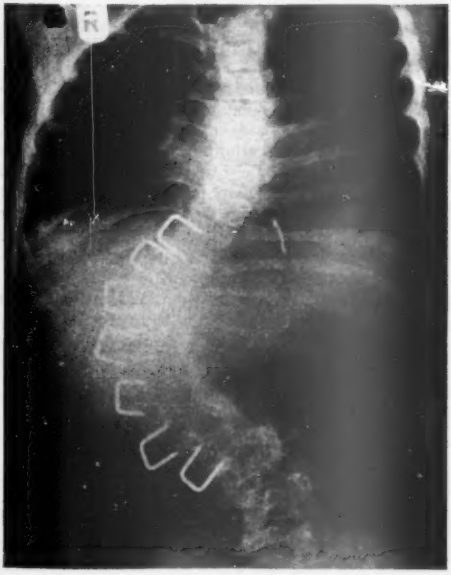

Fig 2B Case 5 *Aged 9*

Case 5 M W, female. Infantile scoliosis. Seven staples. Age 16 months: curve of 20 degrees. Age 5 years (stapled): curve of 40 degrees (Fig 2A). Age 9 years: curve of 65 degrees (Fig 2B).

This curve, like that of Case 4, was adequately stapled and the increase occurred in the stapled area.

As a method of curing scoliosis stapling of the spine, as I have carried it out, has failed. It has even failed to hold a curve where it might reasonably have been expected to do so. It fails because the staples cut through the vertebræ rather like wire through a block of ice. It would seem that the combined stresses and strains produced by movement and growth power are too much for the bone. This shows up in the radiographs by the gradual separation of the staples.

It appears, therefore, that this is a failure of a method and not the failure of a principle, and that the question of whether scoliosis can be controlled by limiting the growth of a vertebra has still to be shown.

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The Surgical Treatment of the Unstable Cervical Disc

by David M Jones FRCS (*Bristol*)

Surgical measures were introduced five years ago to deal with severe cases of cervical spondylosis resistant to the usual forms of conservative treatment. A total of 30 patients has now been treated by operation. The majority of the patients presented clinical evidence of weakness and instability at one or more discs; a lesser number with more or less stable forms of the degenerated disc were operated on to relieve persistent root pain.

Discomfort in the throat is one of the symptoms associated with instability at a disc. The syndrome typically affects women and is sometimes attributed to disorders of a functional or nervous nature. Common complaints are a sense of constriction, of a lump in the throat, or choking sensations, though the patients are aware of no real obstruction on swallowing. These symptoms tend to develop with fatigue, and the influence of posture may be apparent. Stabilizing the weak disc has, without exception, eliminated these unpleasant sensations.

The operative measures have usually been the grafting of weak discs with decompression of sensitive nerve roots by removal of bone overlying the exits of the nerves. Two discs is the maximum number grafted in any patient; of 20 treated by these means all but 3 obtained satis-

factory results. Headaches, giddiness and discomfort in the throat, a triad of symptoms apt to suggest a non-organic basis for these complaints, have invariably been relieved. One case of unusual interest, a man aged 50 with eight years' history of recurrent pain in the neck due to a lesion of the sixth-seventh disc, had typical tennis-elbow at the time of operation. Grafting of the disc and decompression of the sensitive root resulted in immediate and lasting relief from the elbow pain. An unsatisfactory outcome in the 3 cases mentioned was due to deterioration in discs other than those grafted. Decompression of nerve roots without grafting, performed in 2 cases, did not prove an entirely satisfactory procedure.

Acrylic inlays (Knight 1959) were inserted in a few recent cases. The first of these operations, performed eighteen months ago, concerned a woman of 50 with pain and instability at three consecutive discs. Giddiness was a prominent feature of her case. The marked and sustained improvement following operation encouraged further trials of the method, but more time must lapse before the results can be fairly assessed. Early benefit of varying degree has been a feature of all these acrylic inlays.

A posterior approach to the laminæ was used throughout, a firm wool collar providing adequate support in the immediate post-operative period. Patients sit out of bed on the first day, are encouraged to take a few early steps and are ambulant in the ward by the end of a week. A plaster collar, applied after removal of the stitches, is worn for three months. A few of the earlier cases remained recumbent for the first two weeks, but the regime was abandoned following the death of a patient from embolism on the sixteenth day. With the exception of this one misfortune there were no complications and all the grafts have been successful.

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Spontaneous Fractures of the Shin in the Presence of Knee Deformities

by F T Wheeldon FRCS (*Plymouth*)

Fatigue fractures in the bones of the lower limbs are a familiar phenomenon in the young, and Singer & Maudsley (1954) and Burrows (1940, 1948) and others have reported their occurrence in older age groups. The 3 cases recorded are of very old women who suffered complete fractures of tibia and fibula as they walked on level ground and without severe trauma; they should complete the range of ages in which this lesion can occur. They were respectively 101, 85 and 77 years old. All had suffered from rheumatoid arthritis and had flexion deformities in the knee-joints. Only the third and youngest had had any steroid therapy; she had been given prednisolone 5 mg twice daily for one year.

Each patient developed an aching pain in the shin, for three weeks, nine days and six weeks respectively, before the sudden onset of severe pain as she walked, which marked the development of complete fractures.

It is argued that these are fatigue fractures from the history of aching pain preceding the apparently spontaneous development of complete fractures and suggested that they are produced by the stress of continued weight-bearing with a flexed knee-joint and that their relative completeness compared with such fractures in younger people is due to the senile loss of cancellous bone and the osteomalacia of disuse. The characteristics of fatigue fractures in younger age groups have been fully described, but it is unlikely that senile bones will respond in the same way to a similar situation and we must not look for the hair-line crack and excessive callus of childhood.

Bone, as semi-rigid material, will be liable to fatigue fracture when subjected to a series of bending stresses at one point, and the variable factors are the deforming stress and the fatigue limit of the bone. In these cases the knee deformities prevent the tibia from bearing weight in its long axis and cause the deforming stress, while the fatigue limit of the bone is reduced by the changes due to old age, limited activity and possibly rheumatoid arthritis.

In the discussion which followed this paper several cases of such spontaneous fracture in old age were recalled and in every case the patient had suffered from rheumatoid arthritis, although it was not necessarily active at the time of the fracture and none had had any steroid therapy. The possibility that rheumatoid arthritis causes some more or less permanent change in bone which reduces its fatigue limit must therefore be considered. If this were so, the fractures which complicate steroid therapy may sometimes be due to this combination of deformity with a reduced fatigue limit and made more probable by the increased activity which follows the suppression of the symptoms by the steroid.

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Mr K H Pridie (*Bristol*) presented a film demonstrating **The Treatment of Fractures of the Middle Two-thirds of the Tibia by Means of Küntscher Nails.**

Section of Ophthalmology

President Sir Benjamin Rycroft OBE FRCS

Meeting June 8 1961

Papers

Chorioretinal Heredo-degeneration

by Professor Jules François (*Ghent, Belgium*)

Chorioretinal heredo-degeneration is defined as a hereditary, primary, progressive degeneration affecting the normally developed choroid and retina. A close correlation exists between chorioretinal degeneration and some hereditary degenerations in the central nervous system. There are numerous forms of chorioretinal degeneration, which can be divided into peripheral, macular and cystic. Retinitis pigmentosa is the most important form of peripheral chorioretinal degeneration.

Retinitis Pigmentosa

The characteristic ophthalmoscopic signs of retinitis pigmentosa are well known, with black pigment deposits, chiefly in the equatorial zone, or with a 'pepper and salt' appearance. In some cases the optic disc may show hyaline bodies or drüsen; in others there is macular degeneration, the features of which are sometimes indistinguishable from those of juvenile macular degeneration of the Stargardt type.

Night blindness is the best-known functional symptom of retinitis pigmentosa (Fig 1). The dark adaptation curve is a very high monophasic or a delayed one. In the initial stage it may even be normal and polyphasic; a normal curve is not incompatible with the existence of night blindness, because it refers to global thresholds.

The visual field is characterized by the presence of an annular scotoma, corresponding in localization with the most markedly affected part of the fundus, i.e. the equatorial zone (Fig 2). The scotoma spreads slowly, chiefly towards the periphery, so that finally only a temporal and macular islet of vision remain. The temporal islet succumbs first so that the patient, before becoming totally blind, may have to depend exclusively on macular vision. Visual acuity may still be normal when the field has become tubular; in cases of retinitis pigmentosa complicated by macular degeneration, however, visual acuity is affected early; the visual field is then characterized from the first by the presence of a central scotoma.

Colour vision is always affected; it is reduced to a dichromatic system, known as acquired blue-yellow blindness and readily recognized with the aid of Farnworth's Panel D–15 or 100 Hue (Fig 3). The disturbance in colour vision cannot be recognized, however, with the aid of Ishihara plates or Nagel's anomaloscope, which only reveal a pseudoprotanomalic anomaly quotient.

The pathognomonic functional sign of retinitis pigmentosa is the complete absence of an electro-

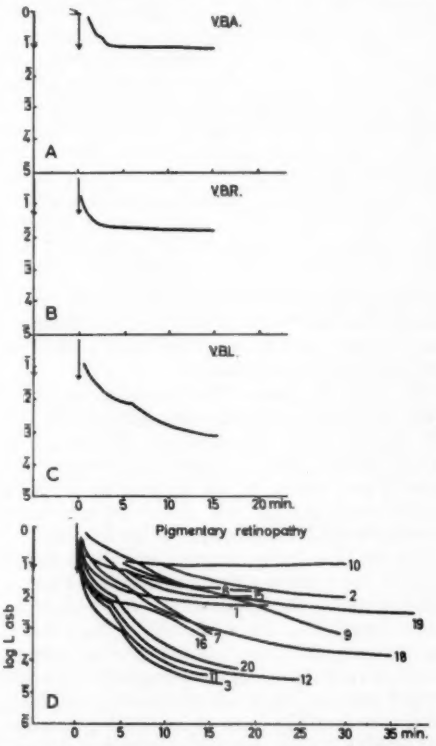

Fig 1 *Dark adaptation curve in retinitis pigmentosa.* A, B; C, *father and his two sons.* D, *14 cases of pigmentary retinopathy*

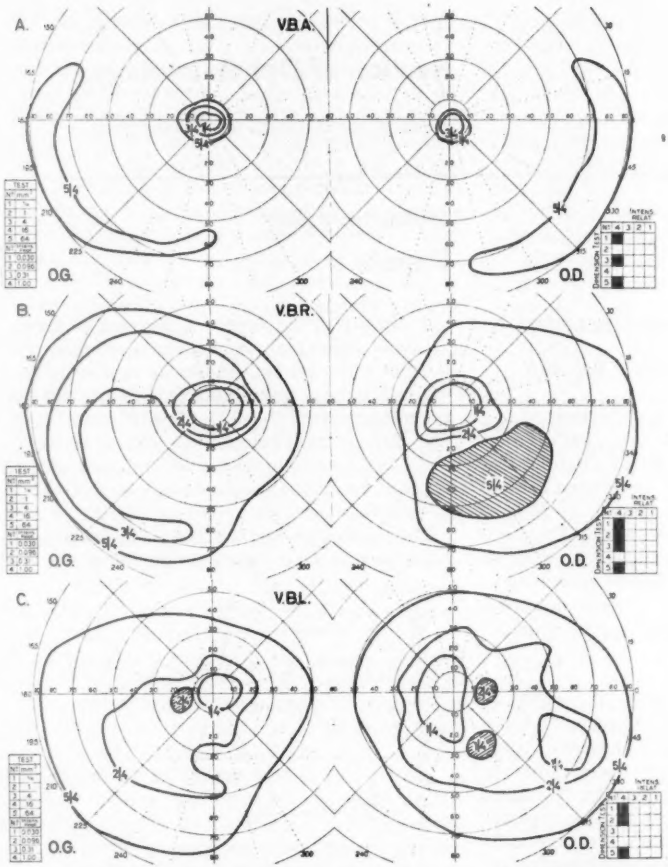

Fig 2 *Visual field in retinitis pigmentosa. Father,* A, *and his two sons,* B *and* C

retinographic (ERG) response (Fig 4). We know nevertheless that very marked stimuli sometimes may produce an *a*-wave, while some mild cases may even show a small *b*-wave.

There are no specific ERG modifications for a given chorioretinal heredo-degeneration. A certain gradation in the electrical disturbance is found, but only with a rough relationship to the severity and extent of the lesions. In localized retinal degeneration the ERG is essentially characterized by a diminution of the *b*-wave.

The use of a strong stimulus permits us to distinguish two types of retinal response: (1) Electropositive ERG: the amplitude of the *b*-wave remains superior to the amplitude of the *a*-wave; the recuperation curve of the *a*-wave remains within normal limits. (2) Electronegative type: the *b*-wave remains below the iso-electric line; these ERGs are found in cases of central degeneration (Stargardt's disease, central pigmentary degeneration, choroidal sclerosis, Sorsby's dystrophy) and in cases of segmentary degenerations.

When the greatest part of the retina is involved, the ERG is much more disturbed. The *b*-wave is always subnormal. The *a*-wave also shows modifications in amplitude and culmination. The ERG obtained by a strong stimulus is always of the electronegative type. The positive *b*-wave tends to disappear and only the following components of the ERG remain: a_1- and a_2-wave and a slow negative deflection. A small positive wave can nevertheless still be present. When using twin flashes, the second ERG is characterized by a slow negative deflection and by a complete absence of *b*-wave. In a further stage, the ERG, obtained by a strong stimulus, presents only a single *a*-wave (culmination time 17 msec) and a slow negative deflection (slow electronegative type). This type of ERG is found in most central and peri-central degenerations, in myopic choroidosis and sometimes in Leber's congenital tapeto-retinal degeneration.

The particular type of ERG found in peripheral degenerations, choroideræmia, Fuchs's

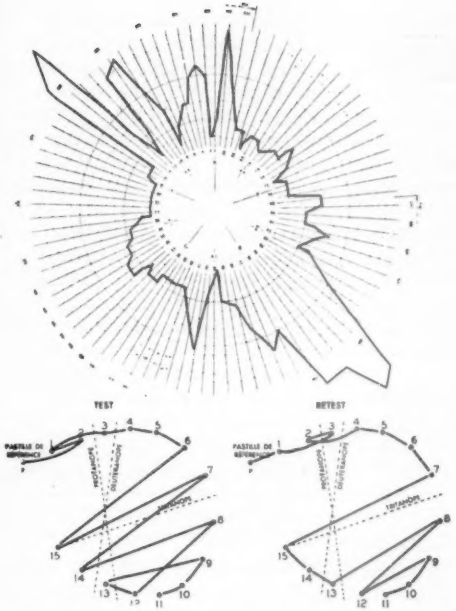

Fig 3 *Colour vision in retinitis pigmentosa: acquired blue-yellow blindness*

gyrate atrophy and in generalized choroidal sclerosis is characterized by an *a*-wave, which is usually subnormal, but sometimes normal in amplitude. The culmination time of this *a*-wave is high (25 to 40 msec), and it is followed by a slow positive deflection with a culmination time of 90 to 130 msec. The recuperation curve of the *a*-wave is very rapid, as compared with normal cases.

The critical fusion frequency (C.F.F.) is variably modified. It is diminished when the *b*-wave disappears. When the *b*-wave is present, even if it is subnormal, the C.F.F. can be relatively high: 30–35. When only the *a*-wave remains, the C.F.F. is low: 18–25. The lowest values are found, when the ERG is of the slow electro-negative type.

We have developed a standardized *electro-oculographic technique*, which makes it possible to study the electrical rest potential of the eye and its decrease during dark adaptation. Retinitis pigmentosa is characterized, not only by rather low absolute values, but also by complete absence of the decrease in potential caused in normal subjects by dark adaptation (Fig 5).

Histological examination in retinitis pigmentosa reveals a series of lesions whose inter-relationships are completely obscure: (1) There is progressive destruction of all nerve-cells, from the periphery inward; the rods are the first to disappear, and this explains the night blindness: subsequently the cones, the external granular layer, the internal granular layer and the ganglion cells are each in turn affected and destroyed. Meanwhile the lost layers are replaced by glial tissue. (2) Lesions affecting the pigment epithelium. Proliferative epithelial nodules pervade even the most superficial layers of the retina and show a marked tropism for the retinal blood vessels, although the epithelium, which remains *in situ*, is more likely to lose its pigment. (3) Lesions implicating the retinal blood vessels. They show marked constriction of the lumen, resulting from hyperplasia of the adventitia. (4) Lesions of the choroid. It may show sclerosis of blood vessels and hyperplasia of the stroma. In other cases, however, the choroid is completely normal.

The white specks sometimes seen on ophthalmoscopic examination are caused by drüsen in Bruch's membrane.

Fig 4 *Electroretinographic responses in chorioretinal heredo-degenerations*

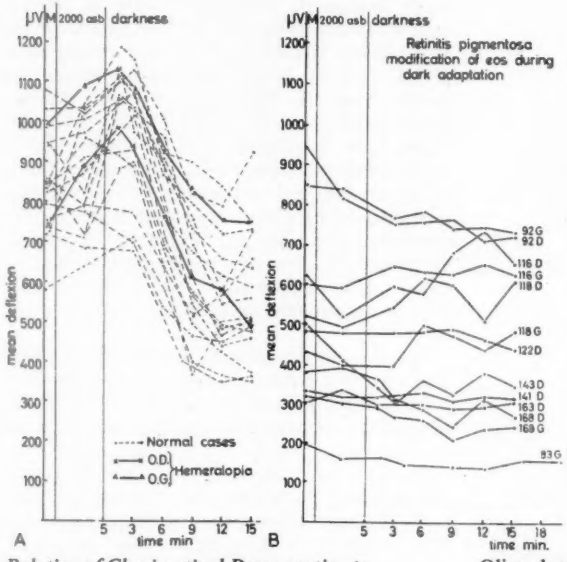

Fig 5 *Electro-oculography.* A, *decrease of the rest potential during dark adaptation in normal eyes.* B, *absence of the decrease in potential during dark adaptation in cases of retinitis pigmentosa*

Relation of Chorioretinal Degeneration to Other Lesions

In other parts of the eye the vitreous body responds to retinal degeneration by complete posterior detachment, but without collapse. This detachment gives rise to visualization of a vitreous opacity immediately anterior to the disc. The lens may show, and very early, a complicated cataract at the level of the posterior pole. In the iris there seems to be a correlation between retinitis pigmentosa and Fuchs's complicated heterochromia. We have seen this association in four cases. It has also been described by Winkler (1940), Franceschetti (1959) and Wolff (1960 personal communication).

Myopia is observed in 50% of cases of retinitis pigmentosa. The refraction curves clearly show that the normal phenomenon of emmetropization no longer exists in the presence of chorioretinal degeneration; this is borne out by the large number of myopic subjects (Fig 6). Whereas myopia of more than 2 diopters is only present in 4·75% of the eyes of a non-selected population, we found it in 35% of 141 eyes with retinitis pigmentosa: the difference is statistically significant ($p = < 0{\cdot}01$).

Keratoconus and glaucoma are slightly more frequent in patients with retinitis pigmentosa than in unselected patients.

Retinitis pigmentosa is very often associated with malformations or diseases of other organs. Complete or partial labyrinthine deafness is diagnosed in about 20% of cases; statistical study has shown that the retinitis pigmentosa and the deafness can be ascribed to the same abnormal gene.

Oligophrenia is diagnosed in 5–10% of cases. This percentage is small, but its significance is increased by the fact that oligophrenia is often observed in the subject's relatives. Epilepsy is relatively frequent in these patients. Their EEGs are often very dysrhythmic and show a low microvoltage. As regards special symptoms, no correlation seems to exist between retinitis pigmentosa and Bremer's status dysgraphicus in so far as this can be considered a clinical entity.

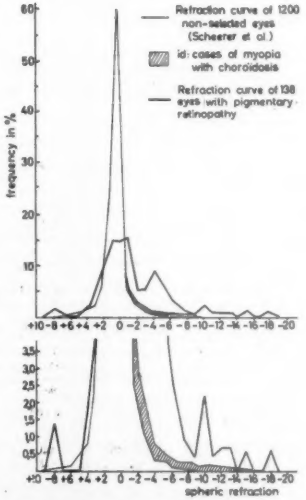

Fig 6 *Refraction curve and myopia in retinitis pigmentosa*

The Bardet-Biedl syndrome is chiefly characterized by typical or atypical retinitis pigmentosa, adiposogenital dystrophy, mental disturbances and polydactylism. The four main symptoms are seldom found in complete combination, not only because some of them are facultative or are replaced by so-called equivalents, but also because the condition develops in its complete form only in homozygotes. The syndrome is caused by an autosomally incompletely recessive gene.

Heredo-ataxia caused by spino-ponto-cerebellar degeneration is sometimes associated with retinitis pigmentosa; but this is exceptional, as the retinitis is seen in only 3% of cases of Pierre Marie disease and is even less frequent in other types of heredo-ataxia.

Another association frequently described is that between retinitis pigmentosa and paralysis of ocular muscles (Barnard & Scholz 1944). This syndrome is sometimes supplemented by ataxia, spastic quadriplegia or atrioventricular block.

The resulting syndrome – retinitis pigmentosa, ophthalmoplegia and ataxia or spastic quadriplegia – is closely related to the Refsum syndrome (retinitis pigmentosa, ataxia and chronic polyneuritis with progressive paresis of the distal part of the extremities). Histopathological findings obtained by Cammermeyer (1956) showed that this Refsum syndrome is a cerebral lipidosis, which brings us to a discussion of the relationship of retinitis pigmentosa and syndromes unmistakably defined as storage or metabolic diseases. There is a marked correlation between retinitis pigmentosa and phosphatide lipidoses. In Tay-Sach's amaurotic idiocy, retinitis pigmentosa is sometimes seen instead of the typical fundus lesions. It is even more frequent in atypical late types of amaurotic idiocy, such as Spielmeyer-Vogt's juvenile form. On the other hand there are families in which Tay-Sachs, Niemann-Pick and retinitis pigmentosa cases occur side by side.

Retinitis pigmentosa has also been observed in cases of cystinuria and cystinosis, Gaucher's disease and Hurler's disease. Alder's leucocyte anomaly, found in a large percentage of cases of Hurler's disease, was also observed in one case of Fuchs's gyrate retinal and choroid atrophy. Alder's anomaly is characterized by the presence of azurophilic granulations in the leucocytes, in our case especially in the neutrophils. The patient, a girl, aged 17, suffered from atrophia gyrata as well as Alder's anomaly. Her parents were first cousins and also presented an isolated Alder's anomaly (which was moreover found in 8 other members of the family in 4 generations). These facts prove that Alder's anomaly can be transmitted in a dominant manner, which has not been previously accepted, and also that the Fuchs's atrophia gyrata chorioideæ et retinæ probably represents the homozygous state of the gene of Alder's anomaly, the isolated presence of which permits the recognition of the carriers of the gene of atrophia gyrata.

The syndrome of Kornzweig & Bassen (1957) combines retinitis pigmentosa with ataxia, cœliac disease, a peculiar erythrocyte malformation known as acanthrocytosis and a significant hypocholesteræmia; it is probably also based on a disturbance in the lipid metabolism and characterized by a disappearance of the β-globulin in the blood serum.

Geographic Distribution and Heredity

Patients with retinitis pigmentosa are found in all parts of the world, and the absolute frequency of the affection fluctuates around 5 per 1,000 in all countries in which determinations were made and which are not characterized by an unusually large percentage of consanguineous marriages. No race is known in which the gene is more frequent. In this respect retinitis pigmentosa differs from other chorioretinal degenerations, e.g. the Tay-Sachs syndrome, which has a remarkably high incidence in Semitic races, and 'malattia leventinese' – a special type of macular degeneration, which is exclusively found in one specific valley of the Ticino.

In Belgium, retinitis pigmentosa is known to be responsible for at least 6% of all cases of blindness; this percentage is undoubtedly below the true value, because atypical forms, e.g. Leber's disease (1869), are insufficiently taken into account. There are reliable statistics for the Netherlands, and it has been established there that Leber's disease causes 5·3% of cases of blindness in adults.

Three different modes of heredity for retinitis pigmentosa are known (Fig. 7). The majority of cases present an autosomal recessive heredity. The parents of the subject affected are often consanguineous, although this has been established with certainty in only 25% of cases. The gene responsible is very widespread and if two unaffected heterozygotes marry one out of four of their children will be affected. Since the absolute frequency of the gene is known (1 : 71), a precise genetic prognosis can be established,

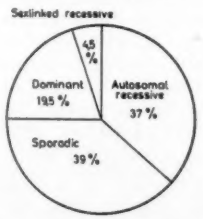

Fig 7 *Heredity in retinitis pigmentosa*

when parents seek advice as to the possibility of retinitis pigmentosa in an expected child. For example, when both parents are affected the child is bound to be affected also; if only an uncle is affected, the risk amounts to only 0·24%. A definite diagnosis can be made very soon after birth on the basis of electroretinographic findings. The second mode of heredity is one of regular or irregular autosomal dominance. Some authors suggest that these cases, too, involve an ordinary autosomal recessive gene, whose action becomes dominant because of coupling into another gene. The course of this condition seems to be more benign; general symptoms are less common in this dominant form.

The third mode of heredity is very rare, but exceedingly interesting (François 1961). It is characterized by intermediary sex-linked recessivity, the males showing retinitis pigmentosa with marked progressive choroidal sclerosis, while the female carriers show no functional symptom, but can be recognized immediately because the fundi show a golden-yellow, glistening reflex, especially in the perimacular region. In a family of 72 members and 4 generations, 5 men were affected and there were 7 female carriers with the tapeto-retinal reflex. One man presented at the same time a segmentary retinitis pigmentosa and tapeto-retinal reflex.

A study of the relative frequencies of the various modes of heredity shows that the sex-linked and the dominant forms are rare as compared with the autosomal recessive form, particularly because the majority of the sporadic cases are in fact also ascribed to autosomal recessivity. Retinitis pigmentosa shows a male predominance, regardless of the mode of heredity. The female sex is invariably less prone to retinitis, so that the heredity may be described as sex-controlled.

In the past few years, much experimental work has been done with the aid of toxins, which selectively affect specific retinal layers. One of the most frequently used substances is iodo-acetic acid, which almost selectively destroys the photoreceptors, and also sodium acetate, which injures the pigment epithelium.

None of this affords any information on the pathogenesis of human retinitis pigmentosa. The majority of authors in recent years have preferred to ascribe the process to 'abiotrophy' or primary precocious ageing of nerve cells, rather than to accept the classic theories of a vascular affection of the choroid or the retina, endogenous intoxication or a diencephalo-hypophyseal affection. It is surprising that no investigator has so far wished to correlate the ætiology of retinitis pigmentosa with metabolic disturbances. Yet such correlations undoubtedly exist.

Related Chorioretinal Degenerations

Retinitis pigmentosa can be atypical in its localization. The retinitis can be macular or perimacular in both eyes; or a certain segment only of the fundus may be affected, the global adaptometric thresholds and ERG findings being virtually normal. Retinitis pigmentosa is always symmetrical, and it is doubtful whether true retinitis pigmentosa could be unilateral. Some thirty reports on apparently verified unilateral retinitis pigmentosa have appeared, but it must be emphasized that these are sporadic cases.

Retinitis pigmentosa can also be atypical in the severity of its lesions. In some pedigrees, individuals may show the typical changes, while others show only discrete fundus changes, e.g. without a single osteoblast. Function in such cases and the ERG response can be normal or subnormal.

Finally, retinitis pigmentosa can be atypical as to the time of onset of symptoms. Night blindness as a rule is noticed during the 10th year of life, while considerable narrowing of the visual field occurs a few years later. One variety of atypical onset is senile retinitis pigmentosa, which does not occur until the age of 50 or 60, and in which choroidal sclerosis is very marked. More frequent and more important is the congenital variety described by Leber (1869); surprisingly, his report was neglected until a monograph by Alström & Olson (1957) and subsequent publications from European countries, demonstrated that so-called Leber's disease is in fact an important cause of blindness. It remained unrecognized because the diagnosis depends upon the study of ERG responses under anæsthesia. But as a rule the fundi show only minimal changes such as the pepper-and-salt aspect (previously ascribed to hereditary syphilis), mild choroidal sclerosis, discrete macular degeneration or even no visible lesions at all. The discs and retinal blood vessels nearly always appear normal. Yet the children affected are always blind or nearly so; like all blind children, they nearly always show a searching nystagmus or, at an older age, pendular nystagmus. The associated ocular symptoms (complicated cataract and keratoconus) and the associated general symptoms (metabolic disturbances) are as frequent as in retinitis pigmentosa in adults. Heredity, too, corresponds with the classic form; it is as a rule autosomally recessive, and only rarely dominant.

Retinitis punctata albescens is characterized by the presence of innumerable white specks in the fundi. The condition is very closely related to retinitis pigmentosa; there are many transitional forms and mixed pedigrees. It is important to know that retinitis albipunctata is sometimes virtually stationary, in which case the ERG findings are normal.

The genetic data (mixed pedigrees) also show that a close relation exists between retinitis pigmentosa and two other rare chorioretinal degenerations, *viz:* gyrate choroid and retinal atrophy of Fuchs, with highly characterized ophthalmoscopic features, and generalized choroid sclerosis with its relatively typical ophthalmoscopic picture.

Choroideræmia, however, constitutes a special biotype. It is always characterized by intermediary sex-linked recessivity. The affected males show congenital or progressive centripetal destruction of the choroid and the retina, whereas the female carriers only show peripheral pigmentations, normally not affecting the functions of the retina.

Among the chorioretinal degenerations chiefly affecting the macula there are two conditions sometimes reminiscent of retinitis pigmentosa: (1) Sorsby's dominant dystrophy, where peripheral pigmentation is also seen. This disease is interesting because the appearance of the lesions is reminiscent of the common chorioretinitis of infections or of vascular origin. The dominant heredity shows, however, that hereditary chorioretinal degeneration is involved. (2) Hereditary macular degeneration: It is well known that the modes of heredity, the ages of onset, the ophthalmoscopic signs and clinical features do not enable us to classify every case of hereditary macular degeneration

The clinical application of a battery of tests for the study of several visual functions gives us a new measuring rod in the estimation of these defects so that we can define and recognize more accurately some types of macular degeneration.

Exudative senile macular degeneration (François 1936): It may not be generally recognized that this is an hereditary condition but the ophthalmoscopic signs are well known since the excellent contributions from Junius & Kuhnt (1926) and from Coppez & Danis (1926). Junius-Kuhnt disease has typical functional symptoms: an acquired blue-yellow-blindness, apathological dark adaptation curve and an electronegative ERG.

Central retinitis pigmentosa is a somewhat rare variety of retinitis pigmentosa: the ophthalmoscopic lesions are typical, including osteoblasts, but they are confined to the macular region or the perimacular area. This form may be distinguished from the generalized form of retinitis pigmentosa by the fact that the ERG for a weak stimulus is not entirely abolished and that the dark adaptation curve is better. The defect of colour vision is the same in both forms, namely an acquired blue-yellow-blindness.

Juvenile macular degeneration sensu strictu: The last-mentioned feature provides the best criterion for distinguishing central retinitis pigmentosa from juvenile macular degeneration *sensu strictu.* Indeed, this affection is characterized by an acquired red-green blindness, which evolves toward achromasy, whilst the photopic luminosity curve shifts from normal to protanopic and finally to the normal scotopic function.

The macular regions seem to be covered by a 'snail track', and under it there are yellowish or brownish patches with black pigmentary dots. In some cases the macular lesions are surrounded by large perimacular, yellowish patches or fibrous strands. The retinal periphery, the optic disc and the retinal vessels are entirely normal.

In addition to the disturbance of the colour sense, the functional symptoms are a reduction of the visual acuity which gradually drops to 1/20 or 1/40, the presence of a central scotoma with smooth slopes, a normal or subnormal dark adaptation curve, and a normal or subnormal ERG. The affection generally begins between the ages of 10 and 40. It never leads to blindness, except in the very rare case, when it is associated with genuine retinitis pigmentosa.

Differential Diagnosis

It should be borne in mind that differential diagnosis between retinitis pigmentosa and acquired diseases of the fundus must be mainly based on ERG examination. Syphilis and some virus infections can cause fundus changes very similar to those of retinitis pigmentosa, but the ERG is usually demonstrable and even remains normal in cases of hyperpigmentation of the fundus caused by rubeolar embryopathy. Structural and functional degenerations of the fundus of exogenous origin are never so complete as genotypical degenerations.

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Total Penetrating Keratoplasty

by Professor Joaquin Barraquer (*Barcelona, Spain*)

Introduction

In the last fifteen years the results obtained in corneal grafting have improved considerably. Without doubt the development of better techniques in surgery and instrumentation is responsible for a great part of this advancement. However, increasing knowledge concerning the conditions of the graft, the selection, the preservation and vitality of the donor material as well as the study of the biological processes that occur between graft and host after transplantation have also played a fundamental role.

Modern anti-inflammatory and anti-allergic therapy enables us to modify or reduce undesirable reactions, inhibit fibroblastic reaction and influence, to a certain extent, the immunological mechanisms. In addition, we have the use of antibiotics for the prevention and the treatment of possible post-operative infections. All these innovations have greatly contributed to the good results we now obtain.

We can classify keratoplasties on an anatomical basis into lamellar or penetrating, partial or total, depending on whether the graft is full thickness or partial thickness and whether it embraces a part or the total diameter of the cornea.

By the term 'total keratoplasty' we understand a keratoplasty which involves the corneal limbus. Thus, it has a diameter of 10 or 11 mm and may be as large as 14 mm which would be equal to the diameter of the anterior chamber.

I have chosen the subject of total penetrating grafts because it raises a range of biological and technical problems which do not present themselves in partial penetrating keratoplasty. The latter give excellent results if the patient is well prepared, if the operating techniques are adequate and if the recipient cornea is in good condition. Unfortunately, the same is not true of total penetrating grafts since in most cases the cornea does not remain clear and may even develop phthisis bulbi. We found that the best result that could be expected with this type of operation was a more or less opaque graft serving a tectonic function, and it was necessary to perform a small partial transplantation at a later date in order to obtain some optical result.

This type of operation is performed in eyes which have already been severely altered by pathological changes and thus present major technical difficulties. The most important difficulty, however, is of biological origin and probably due to tissue incompatibility. The high percentage of successful results obtained with autokeratoplasties seems to confirm this point, the technical problems remaining the same whether the graft is autoplastic or homoplastic, but the results being quite different.

Total Penetrating Autoplasty: Personal Experience

We have obtained very satisfactory results in 6 cases of total penetrating autoplasty performed during the last three years, where 100% transparency of the graft has been maintained.

Case 1 Male, aged 44

Aphakia, endothelial dystrophy, secondary to irrigation of the anterior chamber with a badly preserved adrenaline solution (? phenol) (Fig 1).

Keratoplasty with homoplastic graft without success (Fig 2).

Penetrating autokeratoplasty of 11 mm (Fig 3). The figure shows the continuous edge-to-edge suture and the anterior chamber filled with air.

Result: No change since the time of surgery three years ago, until now (Fig 4).

Case 2 Male, aged 52

Extracapsular complicated aphakia. Anterior synechiæ. Secondary corneal dystrophy.

Penetrating autokeratoplasty of 11 mm with removal of iris and after-cataract. The Flieringa ring maintained the shape of the sclera preventing vitreous loss and collapse of the globe.

Case 3 Female, aged 61

Corneal dystrophy secondary to malignant glaucoma. In spite of the extraction of the lens and a posterior sclerotomy it was not possible to restore the anterior chamber and hypertension persisted.

Penetrating autokeratoplasty of 14 mm with conjunctival graft, wound closure in two planes, a deep corneal plane and a superficial conjunctival plane. The iris was completely removed and at the end of the operation a cyclodialysis was performed.

Case 4 Male, aged 28

Adherent leukoma. Luxated lens.

Autokeratoplasty, removal of iris and lens.

Final result: Some marginal leukomas in the graft were present in the donor cornea.

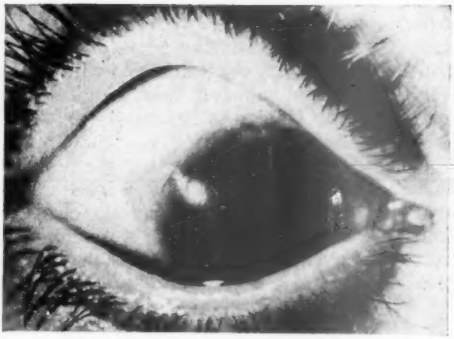

Fig 1 *Before operation*

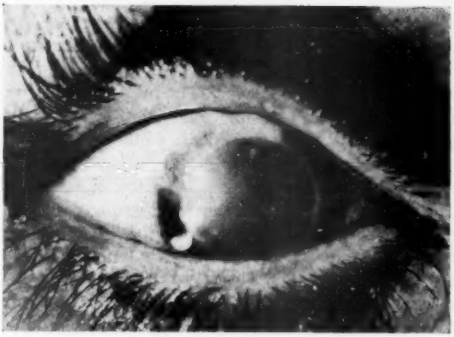

Fig 2 *Keratoplasty with homoplastic material*

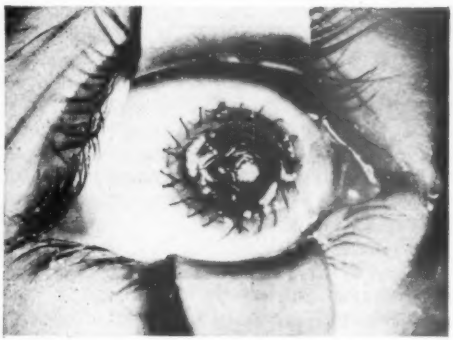

Fig 3 *Autokeratoplasty (11 mm). The graft is secured by a continuous edge-to-edge suture*

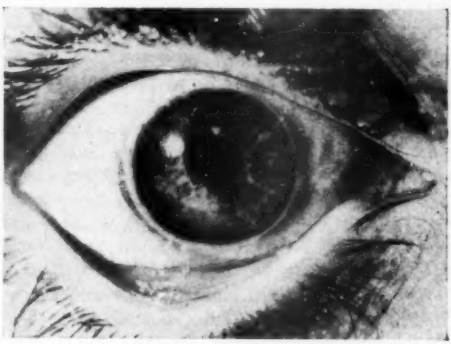

Fig 4 *Result*

Case 5 Female, aged 58

Endothelial dystrophy due to complicated aphakia caused by vitreous loss. Ciliary staphyloma.

Corneo-sclero-conjunctival autoplasty.

Excellent immediate result. After forty days the patient developed hypertension and a cyclodiathermy was performed, producing a total retinal detachment. The graft remains transparent.

Case 6 Male, in the 20s

A case of chemical burns on which I operated in New York in 1957. In spite of significant vitreous loss the result was excellent.

I believe these results demonstrate the advantages of autokeratoplasty.

The restrictive conditions, that is the fact that we can only apply this method to a blind patient who has lost one eye from corneal disease and the other due to a retinal affection, while the cornea is in good condition, should not make us lose interest in this type of operation. In fact, it ought to encourage us to persist in our investigations of the biological aspects of the donor material in order to obtain similar results with homoplastic grafts.

Surgical Technique

(1) General anæsthesia is essential. The operation is long and requires maximum ocular hypotony and complete relaxation of the patient.
(2) Optimum hypotony must be obtained. The use of urea for hypotension gives excellent results.
(3) Collapse of the globe must be avoided. For this reason the routine use of the Flieringa-Bonaccolto ring is recommended. The ring is slightly elevated by the use of two threads, held

by the assistant. Excessive traction must be avoided as it reduces the size of the scleral cavity. The usual precautions must be taken for avoiding compression on the globe by the lid speculum, the palpebral commissure, &c.
(4) When cutting the recipient window the excision line is outlined with the trephine to a depth of one-third of the thickness, and after cauterizing the bleeding vessels the trepanation is continued into the anterior chamber. Complete excision can be achieved with the trephine in keratoplasties with a diameter of 10 or 11 mm; but if the graft is larger, the excision is completed with the Desmarres' scarifier to avoid injury to the ciliary body.
(5) Iris and lens should be removed, except in cases where the iris is completely normal. The lens must always be removed as its presence facilitates the formation of anterior synechiæ.
(6) Fixation of the graft is achieved with virgin silk edge-to-edge sutures. In cases of transplants of 14 mm the incision is covered by a fornix-based conjunctival flap.
(7) *Anti-glaucoma operation:* After the anterior chamber has been filled with air, a small cyclodialysis is performed. Since the anterior-chamber angle is completely altered, these eyes are bound to develop post-operative hypertension without this complementary operation.

Professor Barraquer showed a film entitled **Reconstructive Keratoplasty**, which illustrated the details of the operative technique employed.

Joint Meeting May 26 1961
with the North of England Ophthalmological Society at the General Infirmary Leeds

Professor J François (Ghent) gave a lecture on **Late Relapse of Congenital Ocular Toxoplasmosis** (to be published in the *Transactions of the Ophthalmological Society of the United Kingdom*)

The following cases were shown:
(1) **Three Cases of Malignant Melanoma of the Choroid Treated by Light Coagulation**
(2) **Laurence-Moon-Biedl Syndrome**
(3) **Keratitis Sicca from Lupus of Face**
(4) **Recurrent Bilateral Exudative Retinal Detachment**
(5) **Progeria**
(6) **Two Sisters with Bilateral Buphthalmos**
(7) **Angioma of Orbit**
(8) **Two Recent Cases of Simple Detachment of the Retina**
(9) **Still's Disease**
Mr George Black

(1) **Series of Anterior Chamber Implants**
(2) **Toxacara canis**
(3) **Intracorneal Foreign Body**
(4) **Lid Amblyopia**
Mr D J Thornton (for Mr John Foster)

(1) **Pseudodoptosis**
(2) **? Tumour of Iris**
(3) **Unusual Lacrimal Swelling**
(4) **Posterior Lenticonus**
(5) **Series of Retinal Cysts**
Mr J Sherne

Correction

Anticoagulants in the Treatment of Retinal Vein Thrombosis
by B Thorne Thorne MB MRCP DO (*Brighton*)
Proceedings **54**, 856, October 1961
Method of Treatment (page 857, column 2, line 3): When warfarin was used, the preparation given was warfarin sodium (Ward, Blenkinsop) and not Marevan.

Section of Surgery

President Lambert C Rogers CBE VRD FRCS

Meeting June 7 1961

Surgery of the Pancreas
[*Abridged*]

Dr Kenneth W Warren (*Boston, Mass., U.S.A.*)

It is only in the past quarter century that diseases of the pancreas have been attacked with vigour and with increasing understanding by surgeons. Although dramatic advances have not characterized this modern era of pancreatic surgery, some genuine progress has been made. Some of the trends in pancreatic surgery will be discernible in a consideration of (1) pancreatic cysts, (2) chronic relapsing pancreatitis, and (3) peri-ampullary carcinomas.

PANCREATIC CYSTS

The temptation to employ a single surgical manœuvre in the management of pancreatic cysts is minimized when they are seen in sufficient numbers. The choice of an appropriate surgical procedure must be individualized according to the ætiology, size, location, duration, visceral relationships, the presence of infection or of neoplasia, and by the general condition of the patient.

Since the great majority of pancreatic cysts occur as complications of acute pancreatitis or upper abdominal trauma, the diagnosis is rarely difficult. Cysts secondary to acute pancreatitis are to be suspected when a mass appears from five to fourteen days after the onset of an attack of pancreatitis or following a shorter interval subsequent to severe blunt trauma to the upper abdomen. The mass may be demonstrated by clinical signs or by roentgenographic evidence, utilizing barium contrast studies of the stomach or colon which show displacement or distortion of these viscera.

Surgical treatment: Pancreatic cysts may be treated by simple drainage, marsupialization, internal drainage, sphincterotomy, enucleation, excision, distal pancreatectomy, pancreaticoduodenectomy or total pancreatectomy. A distinct trend toward the internal drainage of pancreatic cysts is discernible.

When the cyst is large and is associated with severe inflammatory reaction or is densely adherent to adjacent viscera, total excision or resection of the involved segment of the pancreas may be unduly hazardous. Occasionally, the patient is too ill to permit definitive treatment even though the local condition warrants a more radical approach.

A search should be made for secondary loculi and a biopsy specimen for frozen section should be obtained from all suspicious areas. Marsupialization should be avoided because of the skin irritation which results from this procedure. If external drainage is employed, a de Pezzer catheter is sutured into the cystic cavity and the end of the catheter is brought out through a stab wound at an appropriate site on the abdominal wall. This method eliminates the skin irritation completely.

Types of pancreatic cysts: The pathologic varieties of pancreatic cysts observed at the Lahey Clinic are tabulated in Table 1. The high incidence of retention cysts (53) reflects the large number of patients seen with chronic relapsing pancreatitis associated with pancreatic cysts. Particular emphasis should be placed upon the observation that 20 (13·5%) of the 148 cysts reported in this series were neoplastic or resulted from a proximal malignant tumour.

Table 1

Number and type of pancreatic cysts in Lahey Clinic series (148 cases)

Pathology		*Number*
Total pseudocysts		71
Postinflammatory	55	
Posttraumatic	8	
After previous drainage elsewhere	8	
Retention cysts		53
Cystadenocarcinoma		12
Cystadenoma		6
Secondary to carcinoma		4
Angiocysts		1
Congenital cysts		1

Operative Procedures in Pancreatic Cysts

Pseudocysts: Of 71 patients with pseudocysts treated surgically, external drainage was employed in 32 and internal drainage in 14. Sphincterotomy was utilized in 5. The cyst was excised in 8 instances, distal pancreatectomy was performed in 9 cases and pancreaticoduodenal resection in 3. In the majority of pseudocysts either internal or external drainage is preferred. Internal drainage is employed when the cyst is large and when it is adherent to the posterior wall of the stomach. When internal drainage is elected, particular care is exercised to ensure that the cyst is not neoplastic. Sphincterotomy has been used occasionally when the cyst has been related to chronic relapsing pancreatitis. Distal pancreatectomy is the favoured procedure in the treatment of recurrent cysts secondary to trauma. Occasionally a pseudocyst of inflammatory origin may be treated in this manner. Pancreaticoduodenal resection is reserved for the patient with far-advanced chronic relapsing pancreatitis and when the pseudocyst is but one of the manifestations of the chronic pancreatitis.

Retention cysts: External drainage was employed in 5 cases, internal drainage in 4 and sphincterotomy in 12. Ten of these cysts were excised, and 9 were treated by distal pancreatectomy. In 10 cases pancreaticoduodenectomy was performed, and in 1 patient a total pancreatectomy was employed. Internal and external drainage is used less frequently in the management of retention cysts. Excision, distal pancreatectomy or pancreaticoduodenectomy is preferred in a large percentage of retention cysts because they frequently result from chronic relapsing pancreatitis.

Table 2

Pancreatic cysts – operative procedures, all types

Operation	*Number*	*%*
External drainage	41	27·7
Internal drainage	27	18·2
Distal pancreatectomy	25	16·9
Excision of cyst	24	16·2
Sphincterotomy	19	12·8
Pancreaticoduodenal resection	17	11·5
Total pancreatectomy	3	2·0

Cystadenomas and cystadenocarcinomas: Of the 6 cystadenomas, 2 were treated by excision, 2 by distal pancreatectomy and 2 by pancreaticoduodenal resection. These cysts are frequently large. Indeed, the presence of a large tumour involving the pancreas without evidence of distal spread should suggest the presence of a cystadenoma or cystadenocarcinoma. If no evidence of distal spread is demonstrated the cyst should be excised or resected.

Of the 12 cystadenocarcinomas, 2 were treated by external drainage, 1 by internal drainage, 2 were excised, 4 were removed by distal pancreatectomy, 1 by pancreaticoduodenal resection and 1 by total pancreatectomy. Cystadenocarcinomas are relatively favourable for excision or resection.

A summary of the type of operation employed in the 148 cases of pancreatic cysts is given in Table 2. These data indicate the necessity for individualizing the treatment of pancreatic cysts.

Complications and mortality: No complications occurred in 93 (62·9%) of the cases. Pancreatic fistula occurred in 23·6% and pancreatic abscess or peripancreatic infection in 8·1%. There were 4 post-operative deaths, giving an operative mortality of 2·7%.

Results of surgical treatment of pancreatic cysts: Fifty-one of 71 patients with pseudocysts were living at the time of this survey. Nine had been operated on less than one year previously, 12 from one to three years, 2 from three to five years, 22 from five to ten years and 6 longer than ten years. Twenty of the 71 patients were dead; 6 died less than one year after operation, 4 within one to three years, 8 from three to five years and 2 from five to ten years.

Thirty-nine of the 53 patients operated on for retention cysts were living: 8 had survived less than one year, 8 from one to three years, 11 from three to five years, 5 from five to ten years and 7 were living more than ten years after operation. Fourteen patients have since died: 5 lived less than one year, 3 from one to three years, 4 from three to five years, and 2 from five to ten years.

The survival rates following the surgical treatment of cystadenoma and cystadenocarcinoma are of particular interest. Six cystadenomas were resected: 4 of the 6 patients are well from four to seventy-two months after operation. There was 1 post-operative death and 1 patient died nine years later.

Of the 12 cases of cystadenocarcinoma, resection was performed in 8: 4 patients died within one to five years following the removal of the tumour and 4 are living and well. Seven patients with cystadenocarcinoma were operated on at least five years prior to this study; 3 (42·9%) are well. Cystadenocarcinomas should be excised or resected despite their size, if no evidence of distant metastasis or local invasion is present.

These data regarding pancreatic cysts indicate the variable pathology, the difficulties in appraising these cysts and the need for individualization in the choice of the surgical procedure. The surgical treatment of pancreatic cysts can be done with a low mortality even when a significant number of the cysts require excision, distal pancreatectomy or pancreaticoduodenectomy for their removal.

CHRONIC RELAPSING PANCREATITIS

The most controversial aspect of pancreatic surgery concerns the choice of an appropriate operative procedure in the management of chronic relapsing pancreatitis. The wide variety of surgical procedures advocated in the treatment of chronic relapsing pancreatitis and pancreatolithiasis indicates the diversity of the clinical and pathologic manifestations of the disease and reflects dissatisfaction with the results of many of the therapeutic measures which have been employed. For a number of years Cattell & Warren (1953) and Warren (1961) have advocated more direct procedures in the surgical treatment of chronic pancreatitis.

Ætiology: The precise ætiology of chronic relapsing pancreatitis is unknown. Cholelithiasis, chronic alcoholism, severe trauma to the pancreas and certain familial or congenital deficiencies play a role in the production and progression of chronic pancreatitis. Less common factors, accounting for a small group of patients with chronic pancreatitis, include essential hyperlipæmia and hyperparathyroidism.

Howard & Jordan (1960) believe that a distinction should be made between chronic pancreatitis associated with biliary tract disease and chronic pancreatitis secondary to chronic alcoholism. This distinction may be more apparent than real. Some patients with chronic relapsing pancreatitis have gall-stones and also are addicted to alcohol; others neither have gall-stones nor are addicted to alcohol. In some, the pancreatitis has been present before gall-stones developed.

Variable pathology: The pathologic manifestations of chronic pancreatitis are extremely variable. The structural alterations range from swelling and mild induration of the gland to fibrosis, atrophy, necrosis, cystic degeneration and pancreatolithiasis. Indeed, a panorama of the several pathologic changes may be observed in the same gland. The body and tail of the pancreas may show far-advanced disease while the head remains grossly normal.

The core of these observations is that intrapancreatic obstruction, partial or complete, involving one or both of the major pancreatic ducts is apparently responsible for the continuing or recurrent attacks of pancreatitis. Multiple points of ductal obstruction can be demonstrated frequently in far-advanced pancreatitis.

The role of pancreatography in the delineation of pancreatic ductal obstruction is being evaluated in many quarters, and particularly by Doubilet *et al.* (1955). It has not been employed as a routine procedure at the Lahey Clinic in the evaluation of intrapancreatic obstruction.

Pancreatolithiasis represents a phase in the natural history of certain varieties of chronic pancreatitis. The precise mechanism of the formation of these calculi is unknown.

Pancreatic stones initially occur in the proximal position and subsequent stones appear distal to this point. We have designated the large proximal stone as the sentinel stone, indicating the site of intraductal obstruction. In many instances more than one major point of obstruction is present. Complete fibrotic stenosis of the duct of Wirsung or the duct of Santorini is frequently observed immediately proximal to the sentinel stone.

Clinical features: The clinical features and the pathologic findings demonstrated at operation are frequently decisive in determining the type of procedure employed in a given case of chronic pancreatitis.

In 291 cases of chronic pancreatitis, pain was present in 98% and was the major indication for surgical intervention. Weight loss, frequently of major proportions, occurred in 64%. Diabetes mellitus was obvious in 19% and prediabetic disturbance in glucose tolerance was observed in an additional 14% of cases. Jaundice was present in 19% and a history of jaundice was recorded in an additional 6%. Chronic alcoholism was admitted by 24% of the group and narcotic addiction was present in 25%. Associated cholelithiasis was recorded in 35%, pancreatolithiasis in 31% and peptic ulcer in 15%.

Howard & Jordan (1960) feel that pancreatolithiasis is essentially, but not exclusively, a manifestation of pancreatitis secondary to alcoholism. In their personal series of 32 patients they found all were addicted to alcoholism and that in none was the disease associated with cholelithiasis. Kelley *et al.* (1957), on the other hand, observed that 12 of 31 patients had gall-bladder disease, 15 used alcohol to excess, 17 had previously had attacks of pancreatitis, and 4 had no history of gastrointestinal symptoms. Clinical diabetes was observed in 12 cases. At the Lahey Clinic, alcoholism was recognized in only 46% of patients with pancreatolithiasis. Cholelithiasis was present in 18%. These figures lend support to the contention that the rigid separation of alcoholic pancreatitis from pancreatitis associated with disease of the biliary tract may prove to be misleading.

Surgical Treatment

Pathologic alterations in the biliary apparatus should be corrected. Diversionary operations on the bile ducts are employed only when partial or complete obstruction of the bile duct is present.

Gastroenterostomy, pyloric exclusion or gastric resection is employed only if this operation is indicated in the presence of associated gastric or duodenal pathologic manifestations.

Operations on the sympathetic or parasympathetic nervous system were employed at the

Lahey Clinic in a few cases, but are now seldom used.

Sphincterotomy, as advocated by Doubilet & Mulholland (1956), has gained wide popularity. We have been unable to reproduce the results reported by these authors in a large percentage of cases in which we have employed this procedure. Sphincterotomy, consequently, was combined with transduodenal retrograde dilatation, manipulation and intubation of the duct of Wirsung. The opening of the duct of Wirsung occasionally was observed to be separate from the major duodenal papilla. In 3% of cases the duct of Santorini was the major duct, and obstruction in this duct was responsible for the persistence of the symptoms. In approximately 12% of patients manipulation of the duct of Wirsung can be carried out without a preliminary sphincterotomy. Preliminary choledochostomy is commonly employed, but the common bile duct is not opened if this structure is not enlarged.

To-day, sphincterotomy is used in cases of mild to moderate recurrent pancreatitis, but the duct of Wirsung is probed at the same time. In general, the severity of the disease can be correlated with the demonstration of partial or complete obstruction of the pancreatic duct. In the mild cases obstruction cannot be demonstrated. The transduodenal retrograde manipulation of the major pancreatic duct usually combined with sphincterotomy has given far better results than has sphincterotomy alone. This is the preferred procedure when mild or moderate chronic pancreatitis is present. The hazard of post-operative pancreatitis following this procedure gives rise to a significant morbidity and mortality.

Distal pancreatectomy is primarily indicated in the management of chronic relapsing pancreatitis when the disease is confined to the distal segment of the gland. Distal pancreatectomy has been employed in the clinic in 36 cases: 64% of these patients had had a previous operation and 6% had had a sphincterotomy. Distal pancreatectomy is especially applicable in cases of chronic progressive relapsing pancreatitis resulting from severe blunt trauma to the abdomen. Distal pancreatectomy combined with retrograde drainage of the duct of Wirsung, as advocated by DuVal (1954), should be effective when a single point of obstruction is present proximally. Jordan & Howard (1958) reported less satisfactory results with this procedure. Obviously, this operation will not relieve chronic relapsing pancreatitis when multiple points of obstruction exist within the head of the gland.

Pancreaticoduodenectomy: When multiple points of intrapancreatic obstruction are present in the head of the gland, when the disease is of long duration, and particularly when more limited operations have failed, pancreaticoduodenectomy in carefully selected cases is justifiable. There are instances when total pancreatectomy offers the only prospect of relief in chronic relapsing pancreatitis but the physiologic consequences of complete removal of the pancreas are so severe that this operation should be reserved for those special cases in which innumerable points of intrapancreatic obstruction are demonstrable.

Pancreaticoduodenectomy has been performed in 50 patients with chronic relapsing pancreatitis and total pancreatectomy has been employed in 6 instances. In one case in which pancreaticoduodenectomy had been performed, the distal segment of the pancreas was removed subsequently. Thus, 55 patients in this series have had pancreaticoduodenal resection or total pancreatectomy.

Results of Operations for Chronic Relapsing Pancreatitis

In assessing these results it must be remembered that operations of lesser magnitude have been used in the treatment of patients with the milder forms of pancreatitis while the more extensive surgical procedures have been reserved for those patients who have long-standing and far-advanced disease.

Biliary tract procedures alone: In 37 patients the operation was confined to the biliary tract. Gallstones were present in 65%. The results were excellent in 56% of cases and good in 20%. There was one post-operative death.

Sphincterotomy alone: Sphincterotomy and choledochostomy were employed in 23 patients. The results were good in 50% of these cases.

Sphincterotomy and manipulation of the pancreatic ducts: This combined procedure was employed in 74 patients. The results were excellent in 56% and good in 25%. One post-operative death occurred from pancreatic necrosis.

Distal pancreatectomy was performed in 36 patients. The results were excellent in 51% and good in 31%. There was no post-operative mortality.

Pancreaticoduodenectomy: Pancreaticoduodenal resection was performed in 50 patients with far-

advanced chronic relapsing pancreatitis. There was one post-operative death, giving a mortality rate of 2% for pancreaticoduodenal resection. The results were excellent in 33% and good in 30%. Eleven of these patients have subsequently died. In most instances death was related to chronic alcoholism.

Total pancreatectomy: In 6 patients total pancreatectomy has been employed. Only 1 has had an excellent result but 4 others have obtained good results.

Of the 55 patients who had pancreaticoduodenectomy or total pancreatectomy, 34 (62%) obtained good or excellent results.

The incidence of jejunal ulceration following pancreaticoduodenectomy or total pancreatectomy has been excessive (18%). A more radical gastric resection will have to be employed with this type of procedure or bilateral subdiaphragmatic vagotomy will have to be done.

Effective Surgical Procedures in the Management of Chronic Relapsing Pancreatitis

Effective surgical procedures in the management of chronic relapsing pancreatitis include (1) transduodenal sphincterotomy and retrograde dilatation and intubation of the pancreatic ducts; (2) anastomosis of the duct of Wirsung to the stomach or to a defunctionalized segment of jejunum; (3) distal pancreatectomy, or distal pancreatectomy with caudal pancreaticojejunostomy; (4) pancreaticoduodenal resection, and (5) total pancreatectomy.

PERI-AMPULLARY CARCINOMAS

A distinction should be made between carcinoma arising in the head of the pancreas and carcinoma of the ampulla of Vater, the distal common bile duct and the duodenal mucosa in the peri-ampullary area. The history, pathology and prognosis of these tumours differ greatly.

With increasing experience in the operative treatment of peri-ampullary carcinoma, the range of resectability was determined, the fundamental technical requirements were defined, the morbidity and mortality rates were brought within reasonable limits and the prospects for increasing palliation and cure of many patients with these peri-ampullary tumours were enlarged. The reputation of this operation in the future will depend upon the discrimination with which it is applied, the mastery of the technical requirements for success as judged by reasonable morbidity and mortality rates, and the ultimate demonstration that the procedure so applied will not only afford a measure of palliation but in many instances will offer a reasonable prospect of cure.

Pancreaticoduodenectomy has been performed at the clinic on 272 patients between 1942 and 1961. Sixty-one of these resections were done for benign disease. In 6 cases it was thought that a malignant tumour was present. Peri-ampullary carcinomas were found in 211 cases: 85 resections were performed for carcinoma arising in the pancreas, 81 for carcinoma of the ampulla of Vater, 24 for carcinoma of the peri-ampullary portion of the duodenum and 21 for carcinoma of the intrapancreatic portion of the common bile duct. The mean mortality in the 272 resections was 10·3%, and in the 211 cases of peri-ampullary carcinoma in which pancreaticoduodenectomy was performed it was 11·4%. Details of the results are given in Table 3.

Table 3
Follow-up of cases of carcinoma resected

	Carcinoma of							
	Duodenum		*Common bile duct*		*Head of pancreas*		*Ampulla of Vater*	
Total cases	24		21		85		81	
Operative deaths	4 (16·7%)		3 (14·3%)		10 (11·8%)		7 (8·6%)	
Survived operation	20		18		75		74	
	Died subsequently	*Living*	*Died subsequently*	*Living*	*Died subsequently*	*Living*	*Died subsequently*	*Living*
Total	10	10	9	9	60	15	46	28
<1 year	4	2	6	1	40	6	21	6
1– 3 years	5	4	2	3	17	5	15	5
3– 5 years	0	1	1	1	2	1	6	6
5–10 years	0	3	0	3	1	2	4	5
>10 years	1	0	0	1	0	0	0	6
Suitable for 5-year survival study	10		11		47		48	
Lived 5 years or longer	40%		4 (36·4%)		3 (6·4%)		15 (31·3%)	

Only 6·4% of the patients with *carcinoma of the head of the pancreas* operated on prior to the last five years have survived five years or more. At best, primary ductal carcinoma of the pancreas carries a very serious prognosis. Resection should be done only in those instances in which the tumour is small and well circumscribed and when no demonstrable metastasis is present.

CARCINOMA OF THE AMPULLA OF VATER

Pancreaticoduodenectomy was performed in 81 cases (*see* Table 3).

One of the tragedies of carcinoma of the ampulla of Vater is the failure to make a distinction between a tumour arising in this location and a primary carcinoma of the head of the pancreas. Cattell *et al.* (1959) reviewed the pancreaticoduodenal resections for carcinoma of the ampulla of Vater in those patients whose primary operation was performed at the clinic, thus eliminating from consideration the group with the prolonged delay between the initial recognition of a periampullary tumour and its subsequent resection. Of those patients suitable for five-year follow-up, 52% survived five years or more. It would appear, therefore, that primary carcinoma of the ampulla of Vater carries a comparatively good prognosis. These figures reflect the need for making a precise distinction between carcinomas arising in the ampulla of Vater, the intrapancreatic portion of the common bile duct and the peri-ampullary duodenal mucosa on the one hand, and primary ductal carcinoma arising in the head of the pancreas on the other. The prognosis in the former group is good and the prognosis in primary carcinoma of the head of the pancreas is poor.

Pancreaticoduodenectomy is a reasonable operation for the treatment of carefully selected cases of peri-ampullary cancer.

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Mr Rodney Smith (*London*)

Pancreatic Neoplasms

During the fifteen years, May 1946 to May 1961, I have operated upon 665 patients with pancreatic disease (Table 1) and of these 471 had neoplasms. Table 2 shows the site and type of tumour and the number of cases in which resection was carried out.

Table 1

Major pancreatic surgery 1946–61 (665 cases)

	Cases
Pancreatic neoplasms	471
Chronic and relapsing pancreatitis	165
Pancreatic cyst, fistula, trauma	17
Acute pancreatitis submitted to elective surgery	12

Table 2

Pancreatic neoplasms 1946–61

	Patients	*Tumour resected*
Carcinoma of the head of pancreas, ampulla of Vater, terminal common bile duct	339	100
Carcinoma of the body and tail of pancreas	42	3
Benign tumours of ampullary region	10	10
Cystadenoma, cystadenocarcinoma	7	7
Sarcoma	8	2
Islet cell tumours	32	32
Benign pancreatic tumours	5	5
Secondary involvement of pancreas by carcinoma	28	28
Total	471	187

The uncommon benign tumours of the pancreas or ampulla will not be discussed in detail and secondary invasion of the pancreas by carcinoma, usually of the stomach, is outside the scope of the present discussion.

Carcinoma at the lower end of the common bile duct: The most frequently encountered neoplasm was the carcinoma occurring in the head of the pancreas, ampullary region or terminal common bile duct. In the 339 patients with tumours of this kind the operability rate was 29% and the operative mortality rate was 9%.

A more detailed analysis of the fate of these patients, with particular reference to the type of tumour, should allow some answer to be given to the question 'Is radical resection really worth while?', but first I shall discuss some points in diagnosis, investigation and operative technique which are of interest.

Diagnosis: In 1954 Rob and I reported an analysis of major signs and symptoms in 190 patients with neoplasms of this kind (Rob & Smith 1954). Examination of the clinical features in this larger series confirms the earlier observations that:

(1) Jaundice is seldom painless. In carcinoma of the head of the pancreas pain is likely to be severe and is often the first symptom. Backache is usually more severe than abdominal pain. In carcinoma of the ampulla or terminal common bile duct jaundice may be the first symptom, but some abdominal pain is usually present by the time the patient seeks advice.

(2) Fluctuation in the degree of icterus does not rule out a diagnosis of malignancy. In a fair proportion of ampullary carcinomas the icterus does

wax and wane, and may even disappear completely if the centre of a friable tumour sloughs away.
(3) Testing the stools for occult blood will yield a positive result in nearly all ampullary carcinomas.
(4) A palpably enlarged gall-bladder nearly always means a carcinoma. Failure to find a palpable gall-bladder means nothing for there are many reasons why the gall-bladder may be not dilated, or dilated but not palpable.
(5) Radiography employing a barium meal will yield positive evidence in rather less than 50% of cases.
(6) Cholecystography and intravenous cholangiography are useless if icterus is moderate or severe. Visualization of the bile passages is unlikely if the serum bilirubin is above 1·5–2 mg/100 ml.
(7) Percutaneous transhepatic cholangiography may well yield beautifully clear pictures of the obstructed common bile duct suitable for inclusion in a book or for illustrating a paper. The technique, however, carries a distinct risk and should be employed only rarely and with proper safeguards (Nurick *et al.* 1953, Smith 1956*a*).
Operative technique [a series of operative photographs were shown]: If pancreatoduodenectomy is performed, my own preference is for a one-stage procedure (Smith 1954). If, however, a surgeon who has not as yet resected a tumour of this kind wishes to relieve the jaundice by a first-stage procedure in order to send the patient to a special centre for resection to be performed, the best first stage is a cholecystostomy, placed as far laterally as possible. If pancreatoduodenectomy is not to be performed, the palliative operation most often selected is cholecystojejunostomy.

A few ampullary tumours may be locally resected by the transduodenal route. This is a reasonable procedure to select for a benign pedunculated neoplasm but should not be employed for an ampullary carcinoma unless the tumour is very small and the patient very obese or very infirm.

The most important question of all is whether the radical procedure of pancreatoduodenectomy is worth while. There is no doubt that it is most discouraging for a surgeon to spend several hours resecting a difficult tumour, followed by several anxious weeks negotiating the patient through a troublesome post-operative phase, only for metastases to appear within a few months and this may well occur.

Some surgeons have abdicated completely and reject resection entirely, performing only a palliative short-circuit to relieve jaundice. Others advocate pancreatoduodenectomy for ampullary carcinoma but palliative short-circuit for carcinoma of the head of the pancreas. Superficially there appears to be some statistical evidence in support of this course. Table 3 summarizes the immediate results of resection in 100 patients submitted to pancreatoduodenectomy. The youngest patient was 26, a recently qualified doctor, and the oldest was a woman of 86, operated upon in Johannesburg, who is now 90 and going strong. After successful resection, 14 patients have survived for five years or more, the longest survival being thirteen and a half years, the patient being still well and without recurrence. Of the five-year survivals, 11 patients had an ampullary carcinoma, 2 had a carcinoma of the common bile duct and only 1 had a carcinoma of the head of the pancreas.

Table 3
Carcinoma of the head of pancreas, ampulla of Vater, terminal common bile duct

	Cases	*Deaths*	*Mortality rate*
Carcinoma of the head of pancreas	23	5	21·8%
Carcinoma of the terminal bile duct	26	3	11·5%
Carcinoma of the ampulla of Vater	51	1	1·9%
Total	100	9	9%

My experiences, therefore, are similar to those reported in most other series. An ampullary carcinoma offers a reasonable prospect of resection, a reasonable operative hazard and a reasonable chance of long-term survival. A carcinoma of the head of the pancreas offers a much smaller chance of resection, a considerably higher operative hazard and a very much smaller prospect of long-term survival. Carcinoma of the terminal common bile duct lies somewhere between these two extremes, in terms of immediate and long-term prognosis.

My views upon the place of pancreatoduodenectomy in these tumours can be simply stated. In the absence of metastases I believe in resecting every tumour I can. The reasons for resecting an ampullary carcinoma need not be re-stated (Cattell & Warren 1953, Smith 1956*b*). In my view, to resect a carcinoma of the head of the pancreas may offer the patient a chance of long-term survival only fractionally better than that offered by palliative short-circuit, as many surgeons have claimed, but to assume that short-circuit should therefore always be preferred to resection is illogical and takes no account of the patient's symptoms. A high proportion have, or develop later, severe backache, sometimes quite incapacitating in its severity and resistant to all drugs. If resection can be carried out, the patient may well die just as soon but without this very distressing symptom. There are, of course, other ways of attempting to modify this pain, but local measures *per abdomen*, such as subdiaphragmatic splanchnic nerve section or injection with alcohol, are unreliable, while transthoracic splanchnicectomy,

although more effective, necessitates a bilateral thoracotomy which may well be rejected in a patient already deemed to have an inoperable carcinoma.

Carcinoma of the body or tail of the pancreas is a very unfavourable tumour for resection. Diagnosis is difficult until the neoplasm has extended outside the pancreas and infiltrated into the surrounding cellular planes. Even if resection is possible, the long-term outlook is very poor. I have explored 42 patients with tumours of this kind. Pancreatectomy was possible in only 3 cases and in all 3 widespread metastases were present less than one year after operation.

Cystadenoma, cystadenocarcinoma: Prognosis is very different in these tumours, which grow slowly, often to a very large size, but even if sections establish malignancy beyond doubt, metastasis nearly always occurs only as a late complication and an aggressive policy is amply justified.

Sarcoma of the pancreas is rare. Only two resectable tumours of this kind have been encountered, one a lymphosarcoma, the other a spindle cell sarcoma of vast size, resection necessitating excision of stomach, duodenum, pancreas, spleen and transverse colon. The patient, a woman of 70, survived for eighteen months and then died of metastases.

Islet cell tumours: Thirty-two patients with islet cell tumours have been explored and treated as shown in Table 4.

Table 4
Islet cell tumours (32 cases)

β-cell tumours: One adenoma enucleated	23
Two adenomas enucleated	1
Single large adenoma treated by distal pancreatectomy	4
Single β-cell carcinoma. Distal pancreatectomy	2
Nine β-cell carcinomas. Single hepatic metastasis. Subtotal pancreatectomy. Left hepatic lobectomy	1
Zollinger-Ellison syndrome	
Nine adenomas. Enucleation of three tumours from head and resection of body and tail containing six more tumours	1

Evidence collected in the case of the woman of 32 with the Zollinger-Ellison syndrome showed clearly that the tumours were not composed of α or β cells and that a substance could be extracted possessing a powerful secretory effect upon a denervated gastric pouch, its nature being quite different from insulin, glucagon or histamine, and being similar to gastrin.

Chronic Pancreatitis and Chronic Relapsing Pancreatitis

Dr Kenneth Warren has dealt with this subject in detail and I shall only summarize my own experiences briefly in order to have some basis of comparison between American and British figures. Table 5 shows the operations performed.

Table 5
Chronic pancreatitis and chronic relapsing pancreatitis (165 cases)

Operation	*Patients*
Sphincterotomy	81
Transplantation of common bile duct	8
Pancreatolithotomy	5
Distal pancreatectomy with retrograde drainage of the duct of Wirsung	38
Splanchnicectomy	5
Pancreatoduodenectomy	15
Doubilet's 'split pancreatojejunostomy'	1
Ad hoc operations, usually combinations of above procedures	12

Briefly, my personal beliefs are as follows:

(1) *Sphincterotomy* is effective in some cases of relapsing pancreatitis, but ineffective in chronic pancreatitis if permanent irreversible changes in the gland are present, particularly if there is pancreatic calcification or a strictured duct system.

(2) *Transplantation of the common bile duct* has been performed in some cases of chronic pancreatitis complicated by recurrent jaundice. It has not been employed as a treatment of pancreatitis *per se*, though some surgeons have reported good results.

(3) *Pancreatolithotomy* has in my hands proved completely ineffective in the treatment of pancreatitis.

(4) *Distal pancreatectomy with retrograde drainage of the duct of Wirsung* has, in selected cases, proved most effective. The technique adopted during the last few years has been to secure anastomosis of the duct of Wirsung to the pyloric antrum by a method already described (Smith 1961).

(5) I regard *splanchnicectomy* as a treatment of pancreatic pain, not of pancreatitis.

(6) I am not very attracted by either Doubilet's or Puestow's method of split pancreatojejunostomy (Doubilet 1957, Puestow 1957).

(7) *Pancreatoduodenectomy* is technically difficult but gives excellent results, often in the most severe cases (Smith 1960).

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Section of Urology

President M F Nicholls CBE MCh

Meeting April 27 1961

Prostatectomy under Hypotensive Anæsthesia [*Abridged*]

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A review is presented of a personal series of 2,000 cases of retropubic prostatectomy and endoscopic resection, of which 1,688 were performed under hypotensive anæsthesia. The conclusions have been reached from three main groups: (1) Normotensive anæsthesia, an early group of 248 carefully selected cases. (2) Hypotensive anæsthesia 'all-in' group of 373 cases in which no pre-operative drainage and no permanent suprapubic cystotomies were performed, all full bladders being treated as emergencies or semi-emergencies. (3) A seven-year period of 1,315 cases, entirely unselected, including all geriatric cases. These received pre-operative drainage when necessary, but none was condemned to permanent suprapubic cystotomy.

The hypotensive technique showed a marked diminution in transfusion rate and a low mortality. Blood loss and infection are the two main problems in prostatectomy; this review deals with the former.

It is natural to conclude that the dreaded complications of hypotension due to blood loss would occur in purposely induced hypotension before commencing operation. In practice, this is not so. Hexamethonium (C6) (long-acting four to six hours) was used throughout the whole of this series. Trimetaphan camphorsulphonate, introduced some years later, with an action of only short duration, has not been used. C6 has been the drug of choice as, apart from its value during the operation, the slow rise in blood pressure during the next four to five hours helped to reduce the amount of reactionary hæmorrhage. Pentolinium tartrate has been used during the last year of the series. Its action is very similar to that of C6 and it is thought to be rather more reliable but smaller doses are needed. It is claimed that the problem of blood loss under hypotensive technique has largely been overcome.

Advantages of the Hypotensive Technique

(1) *The time factor:* It allows the longest possible time to persevere with the most meticulous hæmostasis and gives the clearest possible view to the surgeon. The excellent view is most marked when using the retropubic approach. The veins in the retropubic fatty tissue and anterior capsule give little trouble.

(2) *The absence of shock:* This, and the slow pulse beat at the end of operation, with facial pallor and dry skin, indicate success in the technique.

(3) *Marked diminution in reactionary hæmorrhage* during the six-hour post-operative period. This applies pre-eminently to the C6 group of drugs and less so to the trimetaphan group.

Surgical Technique

The retropubic approach is used, the prostatic floor is preserved as much as possible and the ureteric orifices are marked by passing short whip bougies into the right and left ureters. The bar is excised with a semilunar incision using an endothermy cutting knife. The arteries should be pumping and the calibre of the arterial stream should be thin, but sufficiently forceful to enable the actual vessel to be picked up with hæmostatic forceps. Time can be taken at this stage for careful hæmostasis. The free bladder edge is sutured to the prostatic pseudocapsule, using a round-bodied needle and plain catgut. If access is difficult in a fat man with a deeply sunken gland, the boomerang needle may be used. The lateral artery may lie hidden. If the boomerang needle is passed into the lateral wall of the prostatic cavity and levered slightly into the wound, it often brings the hidden vessel into view where it can be picked off.

The hypotensive technique is not one to be undertaken light-heartedly with a strange anæsthetist. Under no circumstances should a bloodless field be demanded and the blood pressure is only a vague index of the success of the anæsthetist. It is wrong for the anæsthetist to feel that he has failed unless he brings the systolic pressure down to 70 or below. In the majority of cases we have worked with a systolic pressure of 90–100, with the patient in variable degrees of Trendelenburg position. The dose of C6 has been varied very considerably by the anæsthetist in accord-

ance with his clinical assessment. A very rough estimation of maximum dose (in milligrams) in a fit man is 100 minus his age.

Surgeon-anæsthetist Relationship

Teamwork is of paramount importance in the hypotensive technique. Impatience on the surgeon's part and trepidation on the side of the anæsthetist when his patient is not fully under control lead to trouble. The anæsthetist must avoid heavy premedication. To mix two or three drugs and bring the patient to the anæsthetic room semiconscious is not advocated. The occasional precipitate fall in blood pressure during simple induction is embarrassing; the hypotensive drug should not be given until the blood pressure has reverted to normal. If the surgeon cannot decide what he is going to do until he has cystoscoped the patient he should try to allow the anæsthetist at least seven minutes to give the drug, to await its action, and have the patient comfortably under control in the Trendelenburg position; he should not open the retropubic space until the anæsthetist is ready.

The surgeon should be prepared to do the endoscopic resection with the patient in the head-down position. The minor disadvantage of standing up to resect is amply compensated by the fact that the surgeon's view is not obscured by blood. In the head-down position, using the valve-cutting machine, the pieces of prostate will tend to fall off the end of the cutting loop, but these can be sucked out efficiently. The anæsthetist must bring the patient back to the flat position for this manœuvre but that is not until the end of the operation. Repeated up-and-down positions with the hypotensive patient make it difficult for the anæsthetist to control the blood pressure. Should the anæsthetist find that he has given too much hypotensive drug, and there has been no unexpected blood loss or heavy premedication to account for it, 200 ml dextran will put him in control again. Pressor drugs are never used.

To compare morbidities between the normo- and hypo-tensive techniques is unrealistic. The results given in this review are therefore presented as mortality rates. The criteria used in this series consist of four main classifications: (1) The location or site, i.e. whether the operation was carried out A, in a nursing home or private wing (segregation), B, in a special hospital (non-segregation, but some selection of admissions) or C, in a group urological department (totally unselected owing to Emergency Bed Bureau). (2) Percentage of acute or acute-on-chronic to interval prostatectomies. (3) Percentage over 80 years of age. (4) Percentage of permanent suprapubic cystotomies.

Site was recognized as important by Sir John Thomson Walker (1930), who recorded a mortality rate of 6·1% among his private patients: among 2,691 patients at a special hospital (St. Peter's, London) the mortality rate was 9·9%, and among 3,451 patients from a general hospital it was 19·5%. My own private cases, collected from the last few years, form a comparatively small but consecutive series of 105 patients, of whom 20 were aged over 80: 19 were acute or acute-on-chronic cases, and 86 were interval prostatectomies. There was 1 death (mortality rate 0·9%). Hypotensive technique was used in every case, nobody was condemned to a permanent suprapubic cystotomy, no blood transfusions were given in this series, no cases were returned with clot retention postoperatively. (The proportion of acute or acute-on-chronic to interval prostatectomies was only 1 : 4.)

The hospital group submitted for review shows a consecutive series of 1,936 cases (plus 60 for the first three months of this year, which have not been added to the figures). These have been divided into three groups (Table 1):

Table 1
Hospital cases

	Cases	*Deaths*	
Group 1: Pre C6 (1948-50) site B			
Transurethral resection	81	3 (3·7%)	5·6%
Retropubic prostatectomy	167	11 (6·6%)	
Group 2: C6 (1951–53) 'all-in', site C			
Transurethral resection	189	11 (5·8%)	9·1%
Retropubic prostatectomy	184	23 (12·5%)	
Group 3: C6 (1953–60) site C			
Transurethral resection	595	27 (4·5%)	6%
Retropubic prostatectomy	720	52 (7·2%)	

Group 1 (Table 2*a*) normotensive, admitted to general surgical wards wherever there was a bed available, before a separate urological department had come into being: Here there was selection of cases by the general practitioner and the house surgeon. The geriatric cases went to the infirmary, where they were dealt with by the medical officers. This represents a well-selected group, a far better risk than the remainder of the series. This approximates to site B.

Group 2 (Table 2*b*) hypotensive anæsthesia, 'all-in', unselected: All cases of retention of urine were operated upon as emergencies or semi-emergencies. Pre-operative drainage was not performed, pre-operative preparation was negligible. These figures include those who might have died during pre-operative preparation with bladder drainage.

Group 3 (Table 2*c*) hypotensive anæsthesia, unselected: No permanent suprapubic cystotomies were performed but a Riches tube was used to drain those bladders considered likely to benefit from a pre-operative period of medical treatment

up to four weeks; they were then operated upon, no matter how great the risk. During this period 63 patients with pre-operative drainage died from medical diseases while in the medical wards and therefore never came to operation and are not included in these figures. This represents a mortality of 4·7%; when this is added to the real mortality of 6% it will be seen that cases in Group 2 (emergencies) were comparable. The percentage of acute or acute-on-chronic was 45–55%. The over-80s responded very well to a hypotensive technique; the mortality of 14·7% is low compared with other published results. Extreme old age is not a contraindication to hypotensive technique.

Blood loss: It is difficult to estimate blood loss in retropubic prostatectomies. Some surgeons can estimate blood loss during operation, but it becomes almost impossible to estimate reactionary hæmorrhage except by clinical judgment and inspection of the drainage urine. In this series I have found that half the blood loss goes into the sucker and half into the swabs. In a large series this has averaged 200 ml. On five occasions only have we used a blood transfusion on the table.

Table 3 demonstrates the marked drop in transfusion rate between normotensive and hypotensive anæsthesia. These transfusions were given generously and in the hypotensive series were nearly always given on the third or fourth post-operative day for a fall in hæmoglobin, this fall being partly due to the hydræmia which often occurs in post-operative cases and partly to reactionary hæmorrhage.

Endoscopic resection: During the years 1952–56 especially, the proportion of endoscopic resections performed was high, since the use of a hypotensive technique makes this procedure simple. Sometimes it was done on far larger prostates than would usually be selected. Many of these patients were big heavy men with pendulous abdomens suffering from grave intercurrent medical diseases and it was estimated that their expectation of life was short.

Table 2

Age group	*No. of patients*	*%*	*No. of deaths*	*Mortality rate %*
(a) Group 1 normotensive (1948–50) site B				
80+	30	12	2	6·7
75–80	49	20	1	2·1
70–75	73	29	5	6·9
–70	96	39	6	6·2
(b) Group 2, hypotensive anæsthesia site C				
80+	65	17	10	15·3
75–80	67	18	6	8·9
70–75	99	26	11	11·1
–70	142	38	7	4·9
(c) Group 3, hypotensive anæsthesia site C				
80+	204	16	30	14·7
75–80	298	23	23	7·7
70–75	342	27	20	5·6
–70	472	36	6	1·3

Table 3
Blood transfusion rate

Pre C6:	92 pints in 248 cases	(37% averaged 1 pint)
Post C6:	132 pints in 1,688 cases	(7·2% averaged 1 pint)

Table 4 may be regarded as an index of failure rate in endoscopic resection. I have little doubt that endoscopic resection for a moderately large adenomatous prostate is not completely curative. From the figures it certainly seems to reduce mortality in old men, whose only alternative would be a permanent suprapubic cystotomy.

Table 4
Endoscopic resection (865 cases)

Year	*No. of cases*	*Those needing further transurethral resection or retropubic prostatectomy up to nine years later*	
1948	28	5	
1949	20	2	
1950	33	6	
1951	70	10	
1952	119	9	
1953	93	9	
1954	96	8	76 Failure rate 8·8%
1955	113	9	
1956	117	9	
1957	68	7	
1958	48	2	
1959	28	–	
1960	32	–	

Hypotensive technique is considered to be of greater value in endoscopic resection than in retropubic prostatectomy. The number of grams removed in this series has varied between 4 and 35. The speed of operation has greatly increased, and it is far easier properly to control the bleeding with the fulgurating button. In the whole of this hypotensive series of 1,688 cases only 5 have been returned to the theatre with clot retention.

We hope to have demonstrated in the poorest risk group from the site C type of hospital that blood loss in prostatectomies has been largely overcome even in the oldest and frailest.

The cardiac case: The figures in decades (Table 2*c*) have demonstrated that extreme old age is not a contraindication to the hypotensive technique. The permanently anoxic patient has to be considered most carefully but the risks are certainly not greater with the technique we have adopted. Those with congestive heart failure definitely benefit from a hypotensive technique and have caused very little worry throughout the series. Owing to imperfections in the case notes it is impossible to give an accurate assessment of the number of patients suffering from pre-operative coronary infarction, but from the numbers alone it is obvious that they have been many and we have concluded that coronary infarction is not a

contraindication. Many patients in this series have suffered from one or more attacks previous to operation. These men in our opinion are safer under the hypotensive technique than the normotensive technique. Blood loss kills a poor myocardium quicker than the hypotensive technique.

Post-operative cerebral complications: Cerebral anoxia leading to permanent incapacity has been remarkable for its absence. It must depend somewhat upon the skill of the anæsthetist and the constant attention paid to the patients during and after operation.

Diverticulectomy: Single or double diverticulectomies are performed at the same time as removal of the prostate in the above series. Diverticula which are fixed and need considerable deep dissection are prone to formation of extravesical hæmatomata and in these cases hypotensive technique has proved of great value.

Atonic bladders: Bladders which have not recovered their tone after an endoscopic resection and two months' bladder drainage, have had variable proportions of the bladder removed and a thorough clearance of the bladder neck. I find this a most successful operation.

During the whole series there were no deaths on the table; the numbers alone should eliminate the element of chance. There has been one case of cardiac arrest three hours after operation.

Nursing: The post-operative management of hypotensive cases should be within the capabilities of any efficient ward sister, provided she is supervised for the first half-dozen cases. The ward nurses have been allocated as a routine in their training as for any other ward. The patient usually leaves the theatre with a systolic pressure of just under 100. He is received in the ward, the curtains are so arranged that the hypotensive cases are placed in adjacent beds and the sister has blocks for the end of each bed and attaches a sphygmomanometer to each patient. She then makes a blood pressure chart at fifteen-minute intervals. A catheter is attached to a polythene bag which hangs at the side of the bed. No bladder washouts are used. Only on the rarest occasion is a small sucking syringe used to promote the flow. If the systolic pressure rises too rapidly the blocks are removed, the aim being to produce a blood pressure chart rising each half-hour until at the end of the fifth hour an approach to normality is reached. Attention to posture and height of the blocks will make a slow and gradual rise to normal blood pressure comparatively easy.

Mortality: In prostatectomy, this is of paramount importance, especially as we wish to encourage patients to come for interval prostatectomy before complications ensue. For this reason I deprecate my experimental years of 1951–52 because it is unnecessary for the urologist to take the blame for deaths unconnected with the operation.

Expectation of life: An extract from the life tables of a large insurance company (Table 5) gives some idea of the expectation of life of the men upon whom we have to operate. The average age in my series is 72.

Table 5
Extract from insurance life tables

Age group	*Will not reach next birthday* %	*Mortality rate in series* %
80–90	23	14·7
75–80	10·5	7·7
70–75	6·6	5·6
60–70	3·6	1·3

Acknowledgments: I am indebted for their co-operation to my three registrars over this last decade, Messrs G G Ferguson, G N Lumb and S Bhattacharya, and to my anæsthetists, Drs A H Grace and J Linacre.

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Dr A H Grace (*Hastings*)

Induced hypotension in surgery has from the first published reports been criticized because it was considered that it would increase the risk of coronary, cerebrovascular, and other vascular disasters. In the April 1952 edition of *Anæsthesia* the editorial stressed the dangers of the method and referred to an article by Hayward (1952), reported in that number. Hayward referred to the various forms of heart disease and stressed the danger of hypotension in all of them. He concluded by saying that in cardiac patients the chief risks during surgery were anoxia and hypotension and that the use of hypotensive drugs should be restricted to cases where a bloodless field was essential to the success of the operation. In 1954 Doyle & Kilpatrick, writing on the methonium compounds in the treatment of hypertension, found that in the majority of patients the reduction of pressure caused a reduction in angina-of-effort pain, and they concluded that this treatment was safe and that cardiac infarction was no more common in patients so treated than in others. In a small proportion of patients anginal pain was produced by the fall in pressure, and in these patients the treatment was discontinued.

Rollason & Hough (1960) discussed the use of induced hypotension in the elderly, basing the discussion on a series of 40 cases of prostatectomy with control ECGs. They found ECG changes suggestive of myocardial ischæmia at systolic pressures below 60 mm Hg, and that pre-existing systolic

hypertension predisposed to these changes. They suggested that systolic pressures should not be allowed to fall below 60 mm Hg or, in the systolic hypertensive patients, below 80 mm Hg. On Doyle & Kilpatrick's (1954) findings that a small proportion of hypertensive patients would develop anginal pain with the fall in pressure, Rollason & Hough (1960) suggested that a reduction of blood pressure in a small proportion of patients might cause a lack of oxygenation of vital organs. Renal function has been found adequate down to systolic pressures of 55 mm Hg and the only danger here would appear to be that of a slowed excretion of drugs at low pressures. The cerebral circulation has been found adequate down to systolic pressures of 50–60 mm Hg, but below this impairment might follow.

This series consists of 1,000 prostatectomies carried out in one urological unit during 1951–61.

The anæsthetic has been uniform throughout – premedication with morphia and atropine only, induction with thiopentone sodium, maintenance with nitrous oxide and oxygen 2 : 1, supplemented with pethidine, relaxation being obtained as required with gallamine triethiodide. All patients are intubated. The hypotensive drug used has been hexamethonium bromide (C6) throughout until the last 80 cases when pentolinium tartrate has been used.

All cases were operated on in the Trendelenburg position with a head-down tilt of about 25–30 degrees, gravity aiding by draining the operative site. The head-down tilt also causes a rise in systolic pressure of some 10–15 mm Hg and a slowing of the pulse. It is felt that this rise in blood pressure and fall in pulse rate adds a safety factor which allows this postural hypotension to be used safely, even in the elderly. It is considered that a heart beating at a slow rate against a reduced peripheral resistance will have considerably less work per minute to perform, and that this will fully compensate for any reduced coronary flow caused by the hypotension.

Every case in the series has had induced hypotension, and no patient has been refused operation because hypotension would be used, since it was recognized that in the elderly it would be impossible to be certain which patient might be in danger of coronary or cerebral disasters.

Dosage of the hypotensive drug has been left as small as possible consistent with producing a fall in systolic blood pressure to about 80–100 mm Hg. It has been estimated by a comparison of the resting pre-operative systolic pressure and that after induction; any significant fall either on premedication or induction calls for a reduction in the dose of the hypotensive drug.

The average dose of C6 used has been 15–25 mg and of pentolinium tartrate 5–10 mg and these doses are reduced on any big fall after induction or in the very elderly or frail. If the dose has been overestimated and the blood pressure remains low post-operatively, intravenous dextran has been used. Pressor drugs are considered liable to cause reactionary hæmorrhage.

Results

Mortality only will be discussed under the four headings in which induced hypotension could have played any part. It will be compared with that of two other series under these headings: (1) Diseases of the lungs. (2) Diseases of the kidneys. (3) Cerebrovascular diseases. (4) Diseases of the cardiovascular system.

There were no deaths during the operation.

Table 1 shows the age distribution in the three series, and reflects the high age incidence expected in a urological unit.

Table 1
Age distribution

	No. in series	*Age in years* 80+	70–79	*Under 70*
Salvaris (1960)	1,200	55 4·6%	381 31·7%	764 63·7%
Ellis & Leatherdale (1958)	340	50 14·7%	142 41·8%	148 43·5%
Present series	1,000	170 17·0%	473 47·3%	357 35·7%

Table 2 shows the overall mortality in the three series and the mortality under headings (1) to (4). The present series is divided into the years 1951–52 and 1953–61. In the first two years immediate prostatectomies were being performed routinely.

Table 2
Mortality in the three series

Series	*No. in series*	*Total deaths*	*Deaths from* *Pulmonary embolism*	*Broncho-pneumonia*	*Ascending pyelo-nephritis*	*Renal failure without infection*	*Cerebro-vascular disease*	*Coronary thrombosis*	*Myocardial failure*
Salvaris (1960)	1,200	76 (6·3%)	3	8	7	1	6	7	12
Ellis & Leatherdale (1958)	340	37 (10·8%)	5	5	6	–	2	5	10
Present series (1951–52)	269	30 (11·0%)	2	3	27	3	5	7	13
(1953–61)	731	50 (6·8%)							

(1) *Diseases of the Lungs*
It will be noted that the figures for pulmonary embolism are no higher in the present series.

(2) *Diseases of the Kidneys*
Ascending pyelonephritis shows a big increase in the present series. Three causes are suggested for this: (*a*) High age groups reflecting more serious pre-existing renal damage. (*b*) Immediate prostatectomies during 1951–52. Eleven of these deaths occurred during these two years out of 259 cases (4%). (*c*) On a significant number of occasions these deaths occurred in groups where the patients were in the ward together. Cross-infection in a urological ward was certainly a factor in this mortality.
Renal failure without infection: Three cases died primarily, it is thought, of renal failure. One of those at post-mortem showed small red kidneys with thin cortex and the kidneys of another showed degenerative changes of the type associated with arteriosclerosis. Post-mortem was refused in the third case. All three showed high pre-operative blood ureas (over 140 mg%) and were in the 1951–52 years.

(3) *Cerebrovascular Disease*
Out of the 5 deaths, 3 had a history of previous cerebral accident. It has been argued that pre-existing cerebrovascular disease is a contra-indication to induced hypotension. In this series there were 40 cases with a previous history of cerebrovascular accident, and 37 survived prostatectomy under induced hypotension.

(4) *Diseases of the Cardiovascular System*
Of the 7 deaths from coronary thrombosis in this series, 4 had had a previous coronary thrombosis. Three of these had very severe coronary disease and possibly should not have been operated on. The fourth was misdiagnosed and died from a ruptured ventricle through a coronary thrombosis eight days old.

In the series, however, there were pre-operatively 31 cases with proved old coronary thrombosis and 37 cases with mild to severe angina of effort. Out of these 68 cases 64 survived operation under induced hypotension.

Out of the 13 deaths from myocardial failure, pre-operatively 2 showed dyspnœa on exertion only, 8 were fibrillating with varying degrees of failure, 1 had angina of effort and 1 had an old coronary thrombosis.

In the whole series 176 (17·6%) showed a varying degree of heart disease, excluding dyspnœa only. Myocardial failure as shown by fibrillation with or without œdema and other signs of failure did not represent a great difficulty. The immediate post-operative condition showed in the main a great improvement, the induced hypotension removing the strain from the left ventricle and increasing oxygenation in the lungs.

Table 3
Pre-operative systolic blood pressure in patients who died from vascular disease

	Deaths	*Normo-tensive*	*Systolic hypertension*	*Diastolic hypertension*
Pre-operative systolic blood pressure in all patients		*470*	*447*	*83*
Cerebrovascular disease	5	2	2	1
Coronary thrombosis	7	4 } 14	2 } 7	1 } 4
Myocardial failure	13	8	3	2

Rollason & Hough (1960) suggested that pre-operative systolic type of hypertension might increase the risk of lack of oxygenation of vital organs. It is only possible from the figures in Table 3 to say that pre-operative systolic hypertension did not appear to increase the mortality risk in this series.

It is suggested that the mortality figures in this series show no increase due to the induced hypotension used throughout the series. Indeed, taking into account the greater numbers of cases in the older age groups, it may be that induced hypotension affords more protection against pre-existing myocardial disease than other methods.

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Meeting May 25 1961
at St George's Hospital, London

The following papers were read:
The Diagnosis and Management of Hypercalciuria
Dr R Nassim (*London*)
The Mode of Presentation of Four Confirmed Cases of Hæmangioma of the Kidney
Mr A Eley (*London*)
Reversible Renal Failure
Professor A C Dornhorst (*London*)

The following cases were shown: (1) **Crossed Renal Ectopia.** (2) **Lymphangioma of the Kidney.** (3) **Bilateral Gummata of the Testes.** (4) **Granuloma of Penis** Mr H F Anderson (*London*)

Section of Radiology

President Frank Ellis MD

Meeting March 17 1961

Modern Radiobiology and the Radiotherapist

by Frank Ellis MD (*Oxford*)

In 1956 a paper was published by Puck & Marcus which heralded a new phase in cellular radiobiology, both experimentally and theoretically. This new knowledge should be incorporated into our thinking about radiotherapy to improve our insight and to improve the lot of our patients. There has been a great increase in our radiobiological knowledge since radiation became of such importance in connexion with warfare and it seems, now, as if the early efforts of radiologists to make radiobiological bricks without factual straw may be improved upon in relationship to the use of radiation for treating cancer.

The Control of Cancer

The predilection of metastases for one organ or another implies a soil-seed type of relationship dependent on biochemical or immunity factors which might well prove eventually to be the basis for controlling cancer. Indeed, some control, but not cure, has been imposed by some hormones and chemical substances on some cancers.

As radiotherapists we are conscious of the fact that surgery and radiation are so far the only means by which cancer has been cured. When we consider the ease with which cells from a cancer are known to pass into the blood stream and the tissue spaces the surprising fact is that cancer is ever cured. In using radiotherapy for treating cancer, if we aim to cure it is by eradicating all the malignant cells. We hope they are all within the volume we are treating and that we shall give a sufficient dose to all parts of that volume to destroy all the malignant cells without so damaging the normal tissue as to cause symptoms.

Cure of cancer implies the inability of all the cancer cells in the body to reproduce. It is accepted that, except in rare instances, the possibility of cure, when distant metastases have occurred, does not exist, but if the cancer does not cause death or cause symptoms during life the patient may be said to have undergone a functional cure. Unfortunately, in most instances, the rate of growth of cancer after its clinical diagnosis is such that it begins to dominate the clinical picture in a relatively short time. It follows that we must consider the question of whether a cancer is curable since the philosophy of treatment of a patient must depend on the answer to this question. From this point of view we must consider first of all if it is curable locally. Cancer spreads from the site of origin by the escape of cells which pass into tissue spaces or into capillary or other blood vessels, the number of which, other things being equal, must be related to the volume of the cancer. It follows that growth, whether locally or in metastases, increases the probability of further metastases.

Survival Curves

For any damaging agents, including radiation, a curve relating cell survival to dose can be drawn, the exact shape of which is very important. A curve of the general shape shown in Fig 1 is often referred to as sigmoid and the curve relating dose to damage is the reciprocal of that relating dose to survival. The true sigmoid curve, as referred to in quantitative work, represents a relationship which becomes a straight line on a probit scale as in the case of pharmacological data. It represents a Gaussian distribution. In the case of radiation the relationship of dose to damage is dependent on the mechanism of the action of radiation and the shape of the curve is not a true sigmoid in the above-mentioned sense. It must be noted that a

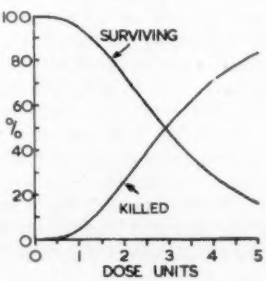

Fig 1 *General form of dose-response curves for cells exposed to damaging agents including radiation*

different curve applies to each set of conditions of dose and that such a curve drawn for single doses may not be the same as that for fractionated doses. Also the curve in the case of fractionated treatment for one overall time may be different from that for another.

If the scale for the survival is made logarithmic, the curve relating dose to survival takes on a different shape (Fig 2). The first part of this graph is curved and the second part is straight. The curved part represents an apparent threshold factor mixed with the lethal effect of the radiation while the straight part is exponential because the proportion of cells damaged by a given dose is constant so that the number of cells damaged by a given dose is proportional at any time to the number present.

Relationship of Reproductive Integrity to Single Dose of Radiation

Much work has been done recently on the relationship of dose to the reproductive integrity of cells (Puck & Marcus 1956, Elkind & Sutton 1959). The cells are cultured in a similar way to that with which we are familiar in connexion with bacteria. A number of cells estimated with known accuracy is plated out on a suitable culture medium using a technique which allows them to be spread evenly and thinly. The number of colonies which grow under suitable conditions of incubation indicates the number of cells capable of reproducing themselves and thus the proportion of the original cell population with 'reproductive integrity' can be estimated. If in a sufficient number of experiments the cells cultured are irradiated a graph can be drawn which relates the dose absorbed to the 'integer fraction' of cells retaining the power of reproduction (Fig 2). This curve has been given relatively precise parameters as a result of a great deal of radiobiological research mainly by Puck and, in this country, by Hewitt & Wilson (1959) of the Westminster Hospital Medical School. The graphs shown here relate the 'integer proportion' to the dose in rads. The 'integer proportion' is the proportion of cells remaining which are capable of reproducing themselves indefinitely and giving rise therefore to colonies of growing cells. The interval between 10^{-1} and 10^{-2} represents a reduction of 90% in the cell population and it is seen from curve C that the dose increase to do this is 375 rads and that it applies at all parts of the curve except the first part where an apparent threshold effect enters in. To produce the first reduction to 10% the dose required is 500 rads. The accepted implication of this higher dose for the initial part of the curve is

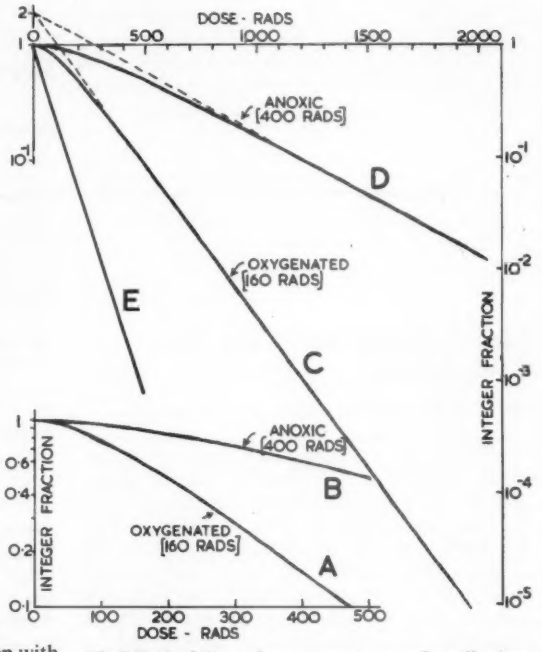

Fig 2 *Typical X-ray dose response curves for cells grown in oxygenated and anoxic conditions. The figure in brackets is the dose increment which on the straight part of the curve reduces the surviving fraction to 0·37 of that obtaining before this exposure (referred to by Lajtha & Oliver as the 37% dose slope). C and D are the dose-response curves for mammalian cells exposed to X-rays under oxygenated and anoxic conditions. A and B are enlargements of the initial shoulders of curves C and D. E is the dose-response curve for cells exposed to α-rays*

that the injury to a cell caused by the radiation is not such as to impair reproductive integrity unless it is added to within a certain time. It is considered that this injury has a 'fading' time of the order of one to three hours and possibly one and a half hours is a reasonable time during which a further injury adds to its effects rather than having to start the process again. It follows also that the lower the dose given the less the efficiency of that dose because the greater is the proportion in it of the threshold part of the dose.

Curve E indicates the state of affairs if one hit or injury to a cell is sufficient as in the case of an injury by a proton, alpha particle or neutron in a chromosome. Under these circumstances there is no apparent threshold and provided a cell is irradiated in the same cell cycle doses are additive, the effect of two or more fractions being the same as that of a single dose of radiation of the same numerical value. Curve D shows that the graph representing doses necessary to produce the same effects under anoxic conditions follows the same

Table 1
Number of cells surviving a single dose (840 rads) which gives 99% killing of oxygenated cells and 77% killing of anoxic cells

Percentage of tumour mass viable cells (10^8 cells = 1 g)	*Tumour diameter (cm)* 0·1	1·0	2·0	5·0
	No. of cells surviving 840 rads			
100% Oxygenated	$5{\cdot}2\times10^3$	$5{\cdot}2\times10^6$	$4{\cdot}2\times10^7$	$6{\cdot}6\times10^{10}$
100% Anoxic	$1{\cdot}2\times10^5$	$1{\cdot}2\times10^8$	$9{\cdot}7\times10^8$	$1{\cdot}5\times10^{12}$
50% Oxygenated	$2{\cdot}6\times10^3$	$2{\cdot}6\times10^6$	$2{\cdot}1\times10^7$	$3{\cdot}3\times10^{10}$
50% Anoxic	6×10^4	6×10^7	$4{\cdot}8\times10^8$	$7{\cdot}5\times10^{11}$
10% Oxygenated	$5{\cdot}2\times10^3$	$5{\cdot}2\times10^6$	$4{\cdot}2\times10^7$	$6{\cdot}6\times10^7$
10% Anoxic	$1{\cdot}2\times10^4$	$1{\cdot}2\times10^7$	$9{\cdot}7\times10^7$	$1{\cdot}5\times10^{11}$
●D Oxygenated	2,600	3,350	4,020	4,460
●D Anoxic	6,460	8,500	10,250	11,400

●D = Curative dose, i.e. total dose required to sterilize 9/10 tumours (50% viable cells)

general form but that the doses required are about 2·5 times as great as under oxygenated conditions.

Table 1 gives quantities taken from the graph of cells killed by various doses. 99% seems a high proportion but it is easy to realize that there may none the less be a very large number of cells remaining.

Summarized Facts Regarding Survival of Reproductive Integrity

Certain facts known in connexion with the work on survival of reproductive integrity of cells are listed below:

(1) The principles implied in the survival curves apply to all the types of cells tested so far.

(2) The dose relationship (i.e. slope of the graph) is said to apply to all types of mammalian cells so far tested both *in vitro* and, for mouse leukæmia, *in vivo*.

(3) As shown by Hewitt & Wilson (1959) an average of 2 cells was required to transplant leukæmia in a certain strain of mice. Using this method as a test of survival of cells they were able to draw a survival curve with a 37% dose-slope value of 160 rads for ^{60}Co gamma radiation as shown by the slope of the graph relating log survival to dose. This figure is virtually true for the slope of the survival curve obtained by Puck and his colleagues plating out irradiated cell suspensions on culture medium. Hence this survival curve is frequently called a Puck-Hewitt curve.

(4) Because of the threshold effect the cells being irradiated appear less sensitive as estimated by the effect/dose ratio with small fractions than with large fractions. For instance, with

100 r – 10% killed Sensitivity = 0·1%/rad
500 r – 90% killed Sensitivity = 0·18%/rad

(5) The extrapolation number varies but is considered, in general, to be proportional to the number of sensitive targets which must be injured in each cell to make it unable to reproduce. Thus, if the straight line portion of the survival curve when produced backwards cuts the vertical axis at 2 there are 2 such targets. If it cuts it at 4 there are 4 such targets. It is clear that the greater the number of such hits necessary to sterilize a cell the greater is the shoulder of the curve and thus the greater the effect on sensitivity of reducing the individual dose.

(6) Recovery from radiation damage is complete as regards reproductive integrity within less than one cell cycle. Surviving cells, in work reported by Elkind & Sutton (1959), had repaired their sublethal damage completely before their first post-irradiation division. (The effect of this on the survival of cells following continuous treatment at about 30 r/h as with radium under clinical conditions is indicated in Table 3. This effect is negligible in the case of dosage rates of 50 r/min.)

(7) 'The system responsible for recovery in surviving cells was not attenuated by repeated exposures' (Elkind & Sutton 1959). Dr Lajtha assures me that so far in all this type of research throughout the world only 1 clone (colony cultured from a single cell) has so far been found with any change (in this case a decrease) in radiosensitivity following radiation and that it is not known if this change was due to the radiation. Moreover, an experiment has been performed in which 94 successive transfers of 1 million tumour cells in mice have been made, separated on each occasion by the administration of 1,000 rads. The radiosensitivity, as indicated by the tumour growth in the 95th group of animals, was unchanged in spite of the fact that the total dose given to the cells implanted and their ancestors since the beginning of the experiment was 94,000 rads.

(8) At doses of 300–500 rads some cells may survive the first cell division, both daughter cells of which may survive one or even two subsequent cell divisions.

(9) It is known also that the presence of dead cells may change the antibody and nutrient background of the intact cells. This factor will not influence the dose-response curve but, if, as a result of giving radiation, a certain number of cells are killed and thus available as nutrient medium for those remaining, it may be that nutritional conditions will be improved, thus giving faster overall tumour growth.

Fractionation of Radiation

If each non-sterilized cell divides before a second fraction of radiation is given, the number of non-sterilized cells is doubled. If the dose given were about 230 rads this doubling would restore the initial number of viable cells. It is convenient to remember that 7 cell divisions will increase the number of cells 100-fold and 10 cell divisions by 1,000 times. It is desirable to give a second fraction before the malignant cells divide but after the normal cells have divided.

Radiation inhibits mitosis as shown by Spear (1953) in chick-fibroblast cultures, and since demonstrated for every cell type so far studied. It is important to know if radiation causes prolongation of the intermitotic interval and whether malignant cells are more affected in this respect than normal cells. In the latter event, to irradiate after the normal cells have divided, fractionation at longer intervals is necessary. It becomes important to know at what interval to apply fractions of radiation so as to irradiate the fixed normal tissue cells at intervals greater than their cell cycle, while attempting to irradiate the malignant cells at intervals less than their cell cycle. At present it seems to be impossible to estimate accurately the cell cycle in any tissue in a patient at any one time. It would be of great value to know this at the time of irradiation both for normal and malignant tissues being irradiated. There is no evidence that the cell cycle can ever change under similar conditions. This could be a legacy from the days when our protozoic ancestors were subjected to the diurnal cycle of the sun in all parts of their minute bodies.

Migration of Cells from Outside the Treated Volume

It seems likely that the normal cell population can be reinforced from outside the volume treated by cells brought in by the blood stream – e.g. histiocytes; capillary endothelium. Such a process could be advantageous in that it would increase the tolerance of the normal tissues by renewing the cell population.

The number of hits needed to sterilize a cell is expressed statistically in the 'extrapolation number' which has already been mentioned. The extrapolation or 'hit number' for mammalian cell lines is mostly 2 but in contrast to this 5–10 has been observed in surviving Chinese hamster cells cultured *in vitro* (Elkind & Sutton 1960). If one hit only were needed to sterilize a cell then, provided fractions of radiation are given within the same cell cycle, the doses are directly additive, i.e. there is no recovery process due to fading of damage. It follows that if the extrapolation number can be reduced to 1 for malignant cells but not for normal cells, then, provided that fractions could be given within the cell cycle of the malignant cell, there would be an added advantage in the sterilization of the malignant cells as compared with the effect of fractionation under ordinary circumstances. Although in cultures bromodeoxyuridine appeared to modify the survival curve to the one-hit variety, an attempt in our centre to use this clinically did not succeed. Being taken up into the nucleic acid of dividing cells the drug could only produce the hoped for effect if it could be incorporated in nearly all the malignant cells before it began to have a toxic effect on other dividing (bone marrow and bowel) cells. The drug is too costly to allow of much repetition.

The use of a low dosage rate but with a dose of the order of 1,000 rads in twenty-four hours for one week as in radium treatments, may allow initial damage in a cell to be supplemented by a second hit before it fades so that the low dose rate as in clinical radium therapy might result in a one-hit type of survival curve although it refers to cells which, with shorter durations of treatment, manifestly require a two-hit mechanism for their sterilization.

Cell Sensitization

A figure which can express the sensitivity of a cell population to radiation is the reciprocal of the log of the integer fraction surviving, divided by the dose in thousand rads, i.e. in the case of a survival proportion of 1 cell per thousand this would be

$$\frac{\log_{10}\left(\frac{1}{10^{-3}}\right)}{1{\cdot}250}=\frac{3}{1{\cdot}250}=2{\cdot}46$$

If we now compare the sensitivity of the oxygenated and anoxic populations for the same survival of 10^{-2} we get for the one

$$\frac{2}{0{\cdot}84}=2{\cdot}38 \text{ and for the other } \frac{2}{2{\cdot}11}=0{\cdot}945$$

The one-hit curve: As shown in Table 2 the dose to reduce the cell population to 1/2 is 145 for the oxygenated and 363 for the anoxic. For a dose of 725 rads the oxygenated population will be reduced to 1/32 while for the anoxic the same dose will cause a reduction to 1/4. The sensitivity in one case is 1·88 and in the other 0·75. If the sensitivity is *doubled* for both graphs the figures are respectively 72·5 and 181·5 and equal halved doses of 362·5 rads will again reduce the populations to 1/32 and 1/4 respectively. If, however, the *same dose* of 725 rads is given – in one case the population reduction is to 1/1024 whereas in the other it is to 1/16.

Table 2

Effects of sensitization – one-hit curve

	Oxygenated cells	*Anoxic cells*	*Ratio*
Normal sensitivity			
50% sensitivity●	1·88	0·75	2·5:1
Dose for 50% survivors	145	363	2·5:1
Fraction surviving 725 rads	$\frac{1}{32}\left(\frac{1}{2^5}\right)$	$\frac{1}{4}\left(\frac{1}{2^2}\right)$	8:1
Double sensitivity			
50% sensitivity●	3·76	1·5	2·5:1
Dose for 50% surviving	72·5	181·5	2·5:1
Fraction surviving 362·5 rads	$\frac{1}{32}$	$\frac{1}{4}$	8:1
Fraction surviving 725 rads	$\frac{1}{1024}\left(\frac{1}{2^{10}}\right)$	$\frac{1}{16}\left(\frac{1}{2^4}\right)$	64:1

● See text for explanation of sensitivity factor

In other words, with 725 rads *without the sensitizer*, in the anoxic population 8 times as many cells remain as in the oxygenated whereas with *double the sensitivity* of both curves there are 64 times as many cells remaining.

Therefore with a sensitizer: (1) For smaller doses in proportion to the sensitizing factor there is no difference from the situation without it. (2) For the same doses as without the sensitizer: (*a*) the effect on both populations is greater and (*b*) the relative effect on the more sensitive population as compared with the other is greater.

It follows therefore in treating a malignant tumour: (1) That a sensitizer can help only if it affects the malignant cells to a greater extent than the normal. (2) If malignant and normal cells are equally affected by a sensitizer then the presence of poorly oxygenated cells in the malignant tumour results in greater malignant cell survival for the same normal cell survival if a sensitizer is used than if not. If *complete oxygenation* of the anoxic cells can be obtained all the tumour and the normal cells would have equal and maximal sensitivity which would probably be greater in the ratio of 1·2:1 than that of the normal tissue under ordinary treatment conditions. Although theoretically possible it is difficult to know if this can be realized in practice because of unknown features of capillary blood flow.

Equalization of Sensitivity by Anoxia

The suggestion has been made by Dr E A Wright that the reduction of oxygen tension to zero will be more likely to produce a uniform sensitivity although doses of about 2½ times will be required. Complete anoxia is obviously a dangerous state but if, as Dr Wright says, the cells of the C.N.S. can tolerate a time of the order of a minute without serious damage it might be possible to make use of this method. The proposal is that a patient under anæsthesia has his oxygen supply cut off completely after he has been placed in position for treatment. At the instant when a potentiometer indicates zero oxygen content of the tissues an electron beam is switched on of appropriate energy to deliver a suitable single dose at the tumour (possibly of the order of 4,000 rads in a few seconds) after which the oxygen supply is instantaneously resumed. I hope to try out this type of scheme with a 35 million volt linear accelerator when we have done the necessary preliminary work on tolerance doses of anoxic and normal tissue to electron beams of various cross sections. This technique obviously requires *single dose* or possibly *weekly* treatments.

A *single dose* produces a maximal effect on a certain population of cells and, as previously indicated, needs to be of the order of 4,000 rads to have a 90% chance of sterilizing a tumour only 2·0 cm in diameter (i.e. 4·2 c.c volume) with half of its volume consisting of viable tumour cells *all normally aerated*. This, as a single dose, is too large to be tolerated but the dose to produce the same effect if half the cells were oxygenated and half anoxic would be even larger – about 8,500 rads.

Fractionation reduces the effectiveness of the radiation in two ways: If each fraction is given before a mitosis can occur there is diminished effectiveness of the radiation because of the smaller sensitivity indicated in the survival curve for the first 250 rads. This is due to the fact that 2 hits are necessary on each cell.

When radiation is given, first ionization occurs throughout the cell which consists of large and specialized molecules separated in terms of Ångström units by large distances in water. The production of electrons and positive ions results in various active radicals such as nascent hydrogen and oxygen, HO_2, H_2O_2 and HO with a short lifetime and a limited range of movement which, if they come near enough to the enzyme proteins or nucleic acids produce damage (a hit). Some of this damage appears to be fatal to the cell if reinforced by a second hit before the damage has been reversed or repaired. As already mentioned the time for this repair seems to be less than six hours and its 'half life' has been estimated at one and a half hours. The number of ions produced and the number of cells, both normal and malignant, in any tumour are all very large so that the process is statistical. If the hits were uniformly distributed throughout the cells so that each had 2 hits then all would die. The chances of a cell receiving 2 hits with increasing dose increase exponentially and so the survival curve represents the statistical chance of the cells receiving 2 hits. It follows that the larger a tumour the greater the dose needed to sterilize it.

Tumour Size after Irradiation

Suppose now that a dose of about 200 rads has been given but that, instead of a second dose being given *before*, it is given *after* mitosis has occurred. 190 rads is enough to sterilize 50% of oxygenated cells. In one cell division the number of reproducible cells will be restored therefore to the original number. If the cells sterilized have not yet disappeared, however, the number of cells in the tumour will be increased by 50%, i.e. an increase in tumour diameter by about 15%. If they have disappeared the tumour will seem unchanged.

Repair after Irradiation of Tumours

There is a possibility that cell destruction, by setting free in the tumour the products of cell breakdown, provides a medium which stimulates the

rate of growth (i.e. of mitosis) as has been shown in ascites tumour cells so that, although the facts represented by the survival curve are unaltered, more rapid mitosis may produce an effect of lack of response of the tumour. If cells are destroyed and rapidly cleared away by efficient access of histiocytes while the space is filled with capillaries and fibroblasts to produce organized healing a tumour will appear to respond readily and completely. This type of effect would seem more likely with a small than a large tumour. If the dose given is such as to result in destruction of the tumour cells it is clear that all the normal cells treated will also have been sterilized and so will be unable to take part in the repair process. Fortunately, the normal repair tissues tend to spread into the space left (as histiocytes, fibroblasts and capillary endothelium) but, if the space is large, the process of filling it will be very slow and there are two other possibilities: (1) Fibrous tissue first formed at the periphery of a cavity becomes mature, contracts and interferes with the repair of the inner part. (2) Infection occurs which tends to prevent complete repair until the margins of the infected area are fibrosing and post-radiation endarteritis has developed when the granulation process becomes halted and a radionecrotic ulcer results. For these reasons the normal tissue tolerance is the most important limiting factor except, possibly, in situations where infection is not going to occur.

For very small volumes, complete destruction of the normal cells is less important because of the ease with which tissues outside the treated volume can fill the gap. Therefore, a small tumour, requiring a smaller dose to sterilize it than a large one, may receive a larger dose with complete safety. For large volumes with relatively few cells present as in the case of cells left in tissue spaces after an operation, the dose required to sterilize them may be small because of the small number so that even the limitation in dose imposed by the intolerance of the large volume or, even in these circumstances by the intolerance of the patient, may not be such as to render radiation treatment ineffective.

The normal tissue tolerance must, it appears, depend on one of two factors: (*a*) Mitosis in the volume irradiated, and (*b*) migration of unirradiated cells into the volume irradiated. If the mitosis of the normal cells is at the same rate or slower than that of the tumour cells then the normal tissue must suffer as much destruction as the tumour but can be renewed by the influx of unirradiated cells. If the mitosis of the normal cells is quicker than that of the tumour cells, as seems likely to be the case, then, even without migration into the treated volume, provided that fractionation can be such that mitosis of normal cells can occur between doses while mitosis of malignant cells does not, repair may proceed while tumour destruction is going on. I understand from Dr Lajtha that while for some normal cells the mitotic interval is up to twenty-four hours, for leukæmic blast cells it is over three to five days. Unless, therefore, mitosis is inhibited too much, it might be possible to choose an optimal interval. For several years I have made a practice of giving very old women with carcinoma of breast doses of 500 r to the whole area, weekly, for 7 sessions. The effect has been satisfactory and the reactions relatively small. Perhaps a weekly interval is satisfactory. Fig 3 represents the effect of fractionation on a cell population. Four types of situation are graphically represented in which the cell survival curves for fractionated radiation are given for two types of cell population. In each case the curve for a rapidly dividing cell population (solid line) is compared with that for a slowly dividing population (dotted line). It is considered that the former may correspond to normal cells and the latter to malignant cells. The division of normal cells to repair any type of injury occurs as a response to cell destruction. The first two comparisons, A, show the relative effects of fractions of irradiation on alternate days. In B daily treatments are shown with a gap in treatment after four exposures. C indicates the likely effect of doses of the same magnitude given every third day rather than daily. D indicates the possible effect when the doses are such as to result in a decreasing population of the normal cells which by a feed-back mechanism stimulates the cells to an increased rate of division as in the case of erythropoiesis. In all the above situations the dose-response is the same and only the population turn-

Table 3

Survival of anoxic cells under three different regimes of irradiation, for the same survival of oxygenated cells (Oliver & Lajtha 1961)

250 kV X-ray dose	*Integer proportion*	*Ratio* $\frac{\text{Survival under } N_2}{\text{Survival under } O_2}$
2,740 rads single exposure	in $O_2 - 7{\cdot}47 \times 10^{-6}$ in $N_2 - 2{\cdot}1 \times 10^{-3}$	3×10^3
13×300 rads (total: 3,900 rads)	in $O_2 - 7{\cdot}47 \times 10^{-6}$ in $N_2 - 1{\cdot}45 \times 10^{-3}$	2×10^3
4,163 rads at 50 r/h (equivalent to 4,900 rads radium at 57·5 rads/hour)	in $O_2 - 7{\cdot}47 \times 10^{-6}$● in $N_2 - 1{\cdot}8 \times 10^{-3}$●	$2{\cdot}4 \times 10^3$

●These values refer to dose response curves calculated assuming 1·5 hours half time for latent damage fading.

Note: Whereas the examples given for the fractionated and continous treatment are practical radiotherapy regimes for large field treatments, the single dose equivalent is greater than would be generally considered permissible

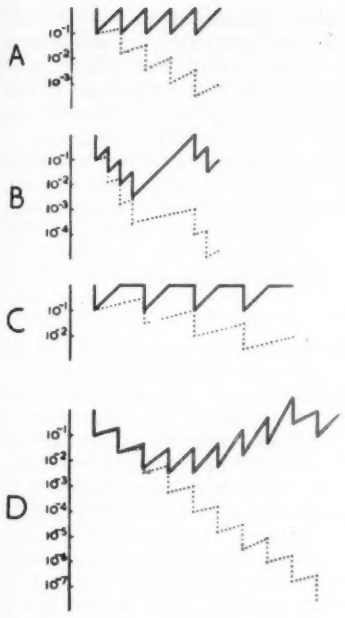

Fig 3 *Effects of different regimes of fractionated radiation doses on two types of cell population. In each case the solid line refers to a fast-growing (e.g. normal tissue) and the dotted line to a slow-growing (malignant) cell population. See text for details*

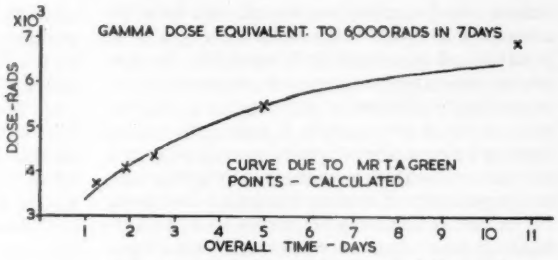

Fig 4 *Relation of total dose and overall time for continuous exposure equivalent to a dose of 6,000 rads in seven days. The curve is due to Mr T A Green of the Royal Northern Hospital, London, and the points have been calculated on the basis of theoretical cell-survival curves*

over time varies. For normal cells a feedback mechanism probably attempts to keep the cell population at the size necessary to fill available space whereas for malignant cells any outside control of this type seems unlikely. Equivalent doses for fractionated schemes calculated from the cell survival curves are shown in Table 3 (Oliver & Lajtha 1961).

Radium or Isotope Treatment: Prolonged Irradiation

Radium may give such a low dosage rate as not to inhibit mitosis and the possibility of a second hit occurring before the damage due to a first hit has faded, can, theoretically, give rise to an apparent one-hit type of survival curve. If the half time for the fading of the damage due to one hit is one and a half hours the curve resulting corresponds fairly closely to a curve which has been produced by Mr T A Green and Mr W A Jennings at the Royal Northern Hospital, London (Fig 4). If mitosis is not inhibited, then survivors from the dose given in one cell cycle being exposed in the next cell cycle to the same dose rate are subjected again to the same hazard. Injury sustained before mitosis by any cell is not expected to persist after mitosis (Elkind & Sutton 1959).

Radium implants, as we know from experience, are well tolerated. It is an advantage that, in the immediate neighbourhood of the needles, the dose is much higher than at the distance at which the dose is calculable. From the relatively low dose areas in a radium implant normal repair cells may spread into the adjacent highest dose areas. Moreover, repair cells may enter *via* the blood stream so that a good circulation, with minimal thrombosis occurring, may be of considerable importance in permitting this not only in the case of radium implants but also in the case of radiation from external sources.

One further point of importance about a radium implant is that the floor of an ulcer or the surface of an ulcerated tumour, likely to contain the least well-oxygenated cells, should be in the high-dose rather than the low-dose region.

Residual Ulcer or Tumour after External Radiation

The practice in using external radiation of giving a higher dose to the last remnant of tumour would seem to be a good one since this is likely to be the site of the least well-oxygenated cells. Instances of this are as follows:

(*a*) Baclesse (1951) does this in treating laryngeal carcinoma.

(*b*) For many years I have used a radium implant to supplement external radiation where practicable. For example, for lymph node residues I have used a line source of radium in a gland, the shape of which fits the isodose curves of the line source. At the margin of the gland a further 4000 rads may be given after a full dose of external radiation; normal tissue tolerance is not exceeded and the middle of the gland, where the cells are least well oxygenated, gets a dose of tens of thousands of rads.

(*c*) After external radiation of an ulcerated breast carcinoma, the condition often improves to leave

only a small ulcer or tumour. A very local excision of this would theoretically seem to be good practice and practically it is successful in cases where more extensive surgery is not desirable.

(*d*) Radioactive colloidal gold may be used to replace the fluid in a necrotic liquefying metastatic node as a means of giving the necessary high dose (in this case with beta radiation) to anoxic cells as a supplement to external radiation. On a number of occasions such glands have been made to clear up even when they have been on the verge of ulcerating.

Radium Combined with External Radiation

It has been my practice for many years to combine radium treatment with external radiation, the idea underlying this combination being to get what I felt from clinical experience were the advantages of radium work with the freedom of external radiation from inaccuracy and inhomogeneity of dose. The result of this combination is to reduce the very high doses and to raise the low doses due to radium only. The very high local doses, within the volume at the surface of which a dose is calculable, seem likely from cell-survival curve considerations to be of great importance in bringing about sterilization of a tumour.

Surgery Combined with Radiation

On the cell-survival facts outlined above certain principles of combining surgery with radiation seem to be justified. After radiation to tolerable doses it seems likely that in a large tumour a large number of malignant cells may remain capable of unlimited reproduction. The outlying tissues are less thickly populated by tumour cells than is the clinical tumour and they are more likely to be well oxygenated and therefore more sensitive. Thus it would seem justifiable to combine radiation with excision to remove those cells still capable of division even though cutting through tissue capable of healing but with possibly no tumour cells capable of indefinite reproduction. The question arises of whether radiation should be pre-operative or post-operative or both.

If a *single dose* of 400 rads is used just *before operation* the number of oxygenated cells in the surrounding tissues through which an incision is to be made and which may contain a few malignant cells among the millions of normal cells will be reduced to 15%. In the tumour itself the anoxic cells will be reduced only to 85%. A given number of cells set free into the circulation during the handling of the operation will have a reduced chance in these proportions of growing as metastases, but careful handling to minimize the number of cells set free is clearly important.

A *course of post-operative radiation* would destroy more of both the normal and malignant cells and improve chances of survival. It is important to start post-operative treatment as soon as possible because, with passage of time, more cell divisions occur and thus the chances of complete destruction of a tumour are reduced, and also collagen replaces fibroblasts and capillaries so that malignant cells may become surrounded by avascular tissue, poorly oxygenated and thus relatively insensitive. It is important, however, that wound healing is complete before radiation treatment is well advanced since, otherwise, the repair cells are sterilized and healing may be prevented.

Post-operative radiation, after the removal of the main mass, seems to have a better chance of success than radiation only. Suppose a tumour of about 5 cm diameter containing a maximum of the order of 10^{11} cells could be given a dose of radiation reducing the cell number to 10^3 viable cells. This would still be a large number from which in 20 cell divisions a tumour of the original size could be produced. The same dose of radiation, equally tolerable by the normal tissues, could, assuming about a total equivalent diameter of 5 mm of malignant tissue, result in local cure if given to the tissues surrounding the operation area.

This reasoning can apply to any tumour, whether primary or metastatic, and it follows that the higher the number of anoxic cells present the greater the need for removal if a local cure is to be arrived at. On the other hand, if too much malignant tissue has to be left behind, there may be no great gain in surgery and there may even be a loss since there is the possibility that the surgery may increase the rate of mitosis of the malignant cells either by local or systemic influence in a similar way to that by which normal repair processes are stimulated to heal by the incision.

A *pre-operative course* of treatment would not be likely to sterilize completely a large tumour mass or extensive palpable infiltration and therefore we must consider that the operation, to be carried out if possible before mitotic division of the malignant cells has recommenced, should be performed by cutting outside any tissue known previously to be infiltrated by neoplasm. Any such tissue is likely still to contain viable malignant cells which may be disseminated and possibly stimulated to activity by an incision.

If a large dose of radiation can be applied locally *at the time of an operation* to a region suspected still to contain cancer it would seem to be a good thing to do. In relatively accessible situations this can be done with *radium or tantalum wire implants* and combined with the usual type of external radiation. I hope to be able to achieve the same purpose by applying a large dose (say

2,000 rads) very quickly with an electron beam to a suspect site at the time of operation on otherwise inaccessible cancer. The energy of the beam can be adjusted to the depth of tissue to be treated to reduce the likelihood of radiation sickness.

From the point of view of *surgical repair* of tissue previously irradiated to a cancer treatment level we must consider that the cells of the normal tissues lie dormant but must divide when damage has to be repaired. If a high proportion of the cells have lost their reproductive integrity the repair processes may be deficient. The deficiency will be aggravated if the damage occurs after six to seven months when the vascular and connective tissue changes due to the radiation have, by fibrosis and endarteritis, so reduced the blood supply and the tissue spaces that non-irradiated normal tissue cells cannot enter the area in as large numbers as normally. Such a situation might, of course, arise as a result of trauma due to infection or injury as well as a surgical procedure. It follows that *early surgery after radiation* has a better chance of successful healing than later and that after six months the conditions are worst. It also follows that a surgical repair of irradiated tissue by a *split skin graft* is best carried out as soon as possible. For instance, if tumour has been removed from antrum or middle ear and radium applied to the cavity, the application of skin to the cavity, other things being equal, would be best carried out one to two days after the radium treatment when the blood supply is least impaired and the unirradiated cells of the graft can take on the prepared surface. To apply a graft before the radium treatment will give it a very poor chance of taking. For cover by *full-thickness skin graft* with an intact blood supply the union should have normal skin at least for one flap. Healing may then occur by first intention, whereas if both flaps have been heavily irradiated they are less likely to heal. Most of the scar tissue under these circumstances is provided by the cells from the unirradiated skin.

Can Tumours be Cured by Radiation?

From the considerations discussed in this paper so far the burning question seems to be 'Can radiation cure cancer?' It is continually reiterated that the only proof of cure is the proved absence of cancer on the post-mortem table. Thus cure can never be proved. What of the patients we know who have lived for many years after radiation? Can we be sure that they will not develop clinical evidence of malignancy at the site treated? The approximate number of cell divisions needed for a tumour to grow from 1 cm diameter to 5 cm diameter is 7, but the number of cell divisions needed to reach 1 cm diameter is 27. In a patient developing a recurrence therefore, even twenty years after treatment, sixteen years of steady growth might have occurred before any tumour could have been appreciated, after which apparent rapid local progress associated with increasing likelihood of metastases may proceed apace. This kind of situation is not uncommon. Nevertheless most radiotherapists would consider that certain tumours may have been cured by radiation. I, for instance, have a patient now about 34 whom I treated twenty-eight years ago for lymphosarcoma of the rectum. Many patients remain well twenty years after treatment but the possibility of complete cure is always open to question. Of course, the same stringent criteria must apply also to surgery. For accurate conclusions the need for continued follow-up and accurate histology even of rodent ulcers seems necessary. However, for what may be considered reasonable treatment and follow up, less rigid criteria need be applied and the judgment of the clinician, whether radiotherapist or surgeon, is important. If, as I have seen in a patient after a radical mastectomy, the development of a 5 cm recurrence has taken twenty-five years and if one considers that this requires at least 34 divisions approximately one can deduce about one cell division per annum. It may be possible that all the cells do not survive. If it is assumed that 75% die for various reasons a rate of 3 per annum may be deduced. If a similar 5 cm diameter tumour can grow in a period of six months then on the same assumptions the likely intermitotic interval would be about two days to one week. Perhaps, by using this type of information, we might be able to decide on an optimum frequency of fractionation since it is logical to aim at a spacing of a maximal number of divisions of the normal cells between fractions, before division occurs of the malignant cells. It is necessary, however, to know more about the frequency of cell division and about the proportion of cells dying both before and after radiation in a malignant tumour.

The *tumour bed* may be very much concerned with the effects of radiation. We must, however, realize that although cells may not be able to grow as well on one medium as on another, the facts about the relative constancy of the dose needed to sterilize a given proportion of cells remain the same. But just as one medium outside the body may promote growth and even result in the death of cells better than another so in the body it may be that the stroma and the diffusible substances present in tissue fluids may have similar influences. In the body, moreover, immune reactions may be influenced by radiation and these may have profound effects on the survival of malignant cells. The association of the presence of lymphocytes in a *lympho-epithelioma* with high radiosensitivity lends point to this suggestion in

view of the gammaglobulin content of the lymphocytes. Moreover, similar considerations might be important in connexion with the very high sensitivity of some reticulosarcomata which appear to be completely cured by doses of 2,000 rads in 4 or 5 fractions.

Some experiments by Murphy which I read about thirty years ago have greatly influenced my thinking. He investigated the effect of radiation on the viability of breast carcinoma cells implanted under the skin of the back in mice. The criterion was the percentage of takes. He showed that a greater effect was produced if the tumour bed and the tumour were irradiated than if either alone was irradiated but that the effect of irradiating the tumour bed before implanting the malignant cells was greater than that of irradiating the tumour cells. Clinically it is a parallel procedure to irradiate pre-operatively the carcinoma and the operation field into which cells might be implanted just before surgery, to the kind of dose used in those experiments.

Radiosensitivity

From the dual consideration of tumour cells and tumour bed we can consider apparent radiosensitivity of a tumour as indicated by its clinical behaviour. If, when irradiated, a tumour shrinks rapidly it is radiosensitive. If it grows bigger or does not shrink at all it is not radiosensitive. While, if it shrinks only slowly or after a long time, it is moderately radiosensitive. The conditions favourable to radiosensitivity are summarized in Table 4.

Table 4
Favourable features

(a) Concerned with numbers of cells capable of reproduction	● Small size of tumour ● Small proportion of anoxic cells ● Small extrapolation number (hit number) of cells ● Steep dose slope of the cells (this may be a constant)
(b) Concerned with the tumour bed	High rate of removal of dead or dying cells High proportion of stromal tissue ● Presence of lymphocytes ● Healthy stroma with good blood supply: (i) not damaged by over-irradiation (ii) not scarred by previous trauma, infection or radiation

● Factors leading to actual tumour destruction

Chemotherapy and Radiation

Chemotherapy is a method of damaging cells by chemical substances which can be used systemically or, by slow or rapid intra-arterial administration with suitable precautions and large doses, regionally. If the effect is on mitotic cells only and those not in mitosis are undamaged, then chemotherapy is different from radiotherapy. If, however, it acts on all the cells so that subsequent cell division is affected as in radiotherapy then its effect is similar. If, however, it is different we might expect a greater effect by combining radiotherapy with chemotherapy than can be achieved otherwise.

In conclusion, considerations of these new cell-survival experiments must influence our thinking about tumours and radiotherapy, providing explanations of our past observations and constructive hypotheses for future work. They underline the need for accurate knowledge of dose given, the need for as high a dose as is compatible with normal tissue tolerance and the desirability of making the dose higher still where there is no normal tissue present as in the middle of a necrotic gland or where severe damage to normal tissue can be tolerated. The necessity for rational, close and continual co-operation between the surgeon and the radiotherapist becomes more obvious both in treating malignant disease and repairing radiation damage. In addition, these suggest that treatment by fractionated methods may require revision. Possibly the most important necessary determination for rational fractionation is of the duration of the cell cycle, especially during a course of irradiation, both for normal cells and malignant cells in individual cases. Dosage inaccuracies in radiotherapy due to poor planning and lack of correction for tissue heterogeneity can be seen to be more important than we have hitherto considered them in relation to the number of cells spared by a 10% or 20% diminution in dose. Similarly, treating all the fields for a given volume at every treatment seems to be of greater importance than has hitherto seemed likely. Finally our basic thinking regarding the management of cancer patients must be modified to fit these new facts. This applies especially to the possibility or otherwise of cure, to the use of ten-year or fifteen-year follow up for assessing the relative merits of two methods, and to the importance of modifying the rate of growth by modifying the soil in which cancer grows.

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Papers

Total Body Irradiation for Organ Transplantation

by M Tubiana, C-M Lalanne and J Surmont
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Since June 1959 we have, in collaboration with the medical teams of Professor Hamburger (Hôpital Necker) and Professor Küss (Hôpital Foch), irradiated 11 patients in preparation for transplantation of a kidney. Two of these cases have already been fully discussed (Hamburger *et al.* 1959, Küss, Legrain, Mathé, Nedey *et al.* 1960).

The aim of irradiating these patients is to diminish the immunological defences of the body and thus make it possible to attempt the transplantation of a kidney taken from another person. A grafted kidney constitutes a very large source of antigens, but it seemed reasonable to hope that if these were confronted by a reduced number of immunologically competent cells, an adaptation could result as the latter multiplied, leading to a state of equilibrium in which the tissues of the host and those of the graft showed a mutual tolerance.

Such hopes were encouraged when it was demonstrated experimentally that histocompatibility is not an all-or-none phenomenon and that acquired tolerances can exist (Ilbery *et al.* 1958, Uphoff & Law 1959). At the same time, observations in Paris on the victims of the Yugoslav accident (Jammet *et al.* 1959, Mathé *et al.* 1959) and on irradiated leukæmic patients (Mathé *et al.* 1959) had revealed the problems involved in the care of persons exposed to high doses of radiation. Finally, the decision to make the first attempt at kidney transplantation after preliminary irradiation was encouraged by the knowledge that a similar technique had just been tried by Merrill and his associates (1960) with results that were not discouraging.

Observation of patients deliberately irradiated in preparation for the transplantation of an organ can yield interesting information on the reaction of the human body to whole-body irradiation. In contrast to what happens in the case of accidents, the conditions of irradiation (dose, dose rate, volume) are known accurately and the dose is uniformly distributed throughout the body. Moreover, hæmatological study of the patients begins before irradiation and no attempt is made to accelerate the regeneration. One reservation must, however, be made from the outset: the observations do not relate to normal subjects but to patients suffering from severe and long-standing renal insufficiency. It is impossible to assess the consequences of this fact, but it is probable that it has less effect on the hæmatological situation than would the presence of a blood disease such as leukæmia.

Techniques of Irradiation

In order to avoid underdosage or overdosage, it is important that the whole of the body should be irradiated simultaneously and in as uniform a manner as possible. If the subject is irradiated alternately with his face and with his back towards the source of radiation, the depth of tissue between the centre of the body and the surface will vary from 5 to 15 cm, depending upon the part of the body exposed. In order to avoid exposure of the superficial tissues to an overdosage, or too large a difference between the doses received at the centre of the body, in thick and in thin regions, it is necessary to choose a radiation beam such that the combined dose delivered by the anterior and posterior beams will vary as little as possible between the superficial tissues and those in the centre of the body, whatever the thickness of the segment considered. This ideal is practically realized with high-energy X-rays or with gamma rays, from a cobalt source.

The technique of irradiation and the dosimetric considerations have been already discussed (Surmont, Dutreix & Lalanne 1960; Surmont, Tubiana & Lalanne 1960) and we shall do no more than recall the results. With the cobalt teletherapy unit used, the distance between the source and the patient is 4 metres. At this distance, the diameter of the field is 1·7 m, but the dose decreases rapidly towards the edges of the field owing to the penumbral effect, and the region in which the dose remains uniform within ±4% is 1·20 m. The whole of the patient's body must therefore be within this area, and the patient is irradiated lying down with the legs flexed. During exposure, the radiation dose to the skin is measured at the sites of entry and exit of the beam (the principal measurements are made on the head, the abdomen, the knees, and the feet). The position of the patient is adjusted so that the dose is as uniform as possible. This is achieved mainly by moving certain parts of the body, such as the head or the lower legs, nearer to or farther away from the source.

In practice, the doses to the interior of the body do not deviate from the mean value by more than ±7% except in certain regions of small bulk, where the deviation may be as much as ±10%. The dose rate in the tissues is about 1·5 rad/min. To avoid fatiguing the patients, however, pauses are necessary, doses of the order of 250 rads being spread over more than three hours, while an exposure of 400 rads takes about 7–8 hours.

Case Histories

During 1959 and 1960, 11 patients were given whole-body irradiation for renal homotransplantation. The observations on the first 2 patients have previously been reported (Hamburger *et al.* 1959, 1960; Küss, Legrain, Mathé & Nedey 1960; Küss, Legrain, Mathé, Nedey *et al.* 1960). Five of the patients died within a few days of the irradiation. We shall not discuss findings in these patients nor the cause of death (post-operative complications or early rejection). One patient died eighteen days after an irradiation which delivered 600 rads, a dose greater than the doses given to the other patients. We shall consider mainly the 5 patients who survived for a much longer period.

Case 1 S, male, aged 37, suffering from chronic renal disease. Blood examination showed an azotæmia, with a blood urea of 345 mg/100 ml and a red cell count of only 2,880,000.

Irradiation was carried out in two sessions; in the first, a dose of 250 rads was delivered to the centre of the body; in the second, six days later, the dose given was 200 rads. Renal transplantation from a non-identical twin was performed on the day following the second irradiation. The fact that the twins were non-identical is evidenced by the absence of physical resemblance and by certain differences in the blood groups. In the red cells, 3 of the 18 phenotypic characters studied showed differences. In the leucocytes, 9 antigens were studied; for 8 the results were identical for the two bloods while 1 was found to be present in the recipient only.

Present condition: Twenty-two months after the operation the kidney is functioning normally and the patient is in good general health. His blood pressure has settled down to almost normal levels, all clinical signs of uræmia have disappeared and the retinal lesions have healed.

Although the twins were non-identical, their twin relationship may have been of some importance, owing to the possibility that mixing of blood took place between the fœtuses. However, skin from the recipient grafted on to the donor was rejected after twenty-five days.

Case 2 C, male, aged 41, had been operated on in 1956 for cancer of the left kidney; cancer of the right kidney appeared one year later. In view of frequent hæmaturia and a blood urea level that had already reached 194 mg/100 ml at the time of operation, his death seemed imminent.

In order not to expose the donor to unnecessary risk it was first ascertained that extirpation of the patient's remaining kidney was not contraindicated by the presence of macroscopic metastases and it was decided to wait until it was certain that there were no serious early complications of this operation before proceeding with the transplantation. Hæmodialysis was carried out on the fourth day to correct the disturbance caused by the anuria. The patient was then irradiated, the dose to the centre of the body being 400 rads; an additional 200 rads at a depth of 3 cm was delivered to the splenic region.

Transplantation of a kidney taken from the non-twin sister of the patient, was performed twenty-four hours later. A difference was found in only 1 of the 11 red blood groups tested, and all 10 white cell antigens were identical.

The patient died five months after operation from a hepatic metastasis. At this time, the kidney was functioning well.

Case 3[2] M, female, aged 22, suffering from chronic renal disease. Transplantation of a kidney taken from the patient's sister was performed. Differences were found in 3 of the 15 phenotypic red cell characters tested. Of the 16 white cell antigens examined, 7 were present in the recipient but not in the donor.

Irradiation was carried out in two sessions: during the first the patient received a dose of 200 rads, and three days later she received a dose of 230 rads. Renal transplantation was performed twenty-four hours after the second session.

Three months after the operation, alterations in renal function prompted us to submit the patient to a second irradiation with a dose of 100 rads delivered to the centre of the body. Fifty days later, the patient died at the end of a four-week period of complete medullary aplasia.

Case 4[1] G, female, aged 26, suffering from chronic renal disease. The kidney transplanted was taken from a man unrelated to the patient.

All the 11 red blood groups tested were identical in recipient and donor; of the 11 white blood groups examined 1 was present in the donor but not in the recipient.

Two months after the operation, changes in renal function necessitated a second whole-body irradiation, a dose of 100 rads being given. The patient is living eleven months after the transplantation and nine months after the second irradiation.

Case 5[2] Y, male, aged 21, suffering from chronic renal disease. The kidney transplanted was taken from his mother. No difference was found between the 15 red blood groups examined; of the 49 white cell antigens examined, 5 were present in the recipient but not in the donor. Five months after irradiation, the patient was still well.

Clinical Results of Irradiation

Immediate reactions: The immediate effects of irradiation are relatively mild. During the actual exposure, when the dose reaches 150–200 rads the patient experiences a sensation of asthenia, with a tendency to nausea, and exhibits tachycardia, pallor, and anxiety. As the patient becomes in-

[1] **Küss R *et al.*** (unpublished observation)
[2] **Hamburger J *et al.*** (unpublished observation)

Table 1
Effects of whole-body irradiation in 5 patients

Case	Dose (rads)	Immediate reactions	Secondary digestive disorders	Hæmorrhagic reactions	Spleen	Hair
1 S	250+200	Nil	Pasty stools from 22nd to 32nd day	Purpura on 15th day	Not palpable	Total loss on 22nd day
2 C	400 with additional 200 to spleen	Vomiting (75 ml) several hours after irradiation. Liquid stools following day	Diarrhœa from 24th to 28th day	Petechiæ on 21st day	Not palpable	Loss began on 16th day. Total baldness on 20th day
3 M	200+230	Vomiting 3 days after irradiation	Nausea from 13th to 24th day. Frank jaundice from 22nd day	Purpura on 15th day	Palpable from 5th day till end of jaundice	Loss began on 12th day
4 G	400 with additional 200 to spleen	Vomiting several hours after irradiation. Nausea for 1 day	Nil	Petechiæ on one thigh (local irritation) on 3rd day, nothing later	Palpable from 18th till 32nd day (maximum on 22nd day); reappeared from 6th to 33rd day after 2nd irradiation	Loss began on 12th day
5 Y	250+200	Vomiting few hours after each irradiation	Nil	Generalized purpura on 15th day	Palpable from 5th during few days	Loss on 17th day

creasingly fatigued, every change in position causes distress and increases the severity of the symptoms. Tolerance to irradiation can be improved by premedication and administration of sedatives during exposure. Paradoxically, the last phase of irradiation is generally better tolerated than the intermediate phase, and, as a rule, the patient is free from reactions during the few hours immediately after exposure.

The part played by psychological factors, such as anxiety, in the production of the reactions is difficult to assess, but the time sequence suggests that it is less important than had been thought.

As can be seen from Table 1 no symptoms could be detected in Case 1 during the first few days after irradiation and the symptoms in the other patients were very slight. During this phase, the general condition of the patients was satisfactory. It should be noted, however, that the major operation performed twenty-four hours after irradiation hinders the study of post-irradiation effects and may mask certain symptoms.

Secondary digestive disorders: These are also of moderate intensity (Table 1) being confined to diarrhœa or slight looseness of the bowels from twenty-five to thirty days after irradiation, and a tendency to nausea during the third week.

Digestive disturbances never presented any real problem in these patients, and feeding by mouth was possible in all except Case 2. In this patient, the reactions were particularly severe, and he had to be fed by intravenous infusion during the period of agranulocytosis.

Hæmorrhagic reactions: No important hæmorrhage was observed in any of the patients. Purpura of the trunk and neck was noted in Case 1 towards the fifteenth day after irradiation, and petechiæ on the inside surface of the thigh on the twenty-first day in Case 2. Purpura was also apparent in Case 3 on the fifteenth day after the second irradiation (i.e. the eighteenth day after the first irradiation). In Case 4, a few petechiæ seen on the thigh on the third day were probably related to local irritation. In Case 5, generalized purpura was noted on the fifteenth day after the second irradiation.

Hair: Loss of hair started in Case 2 on the sixteenth day and was complete on the twentieth day. In Case 5, the loss of hair was complete on the seventeenth day.

In the 2 female patients, Cases 3 and 4, loss of head hair started on the twelfth day. The hair in the armpits and the pubic hair was little affected by irradiation, and they exhibited only slight loss of hair in these regions. In the male patients the beard was unaffected.

Spleen: At no time was the spleen palpable in Cases 1 and 2. On the other hand, in Case 3 the spleen became palpable five days after irradiation; jaundice set in a few days later. The spleen remained enlarged until the jaundice had disappeared. In the other female patient, Case 4, the spleen became palpable from the eighteenth day onwards, reached its maximum size on the twenty-second day, and was no longer palpable by the thirty-second day; it again became palpable six days after the second irradiation and remained palpable for twenty-seven days.

In Case 5 the spleen was palpable after the fifth day for a few days.

While the significance of the enlarged spleen in Case 3 is open to discussion, since she also had an infectious hepatitis, in Cases 4 and 5, there seems to be no doubt that there was a correlation be-

tween the enlargement of the spleen and the irradiation.

None of the patients exhibited either convulsions or neurological disturbances.

Hæmatological Findings

Erythrocytes: The changes in the red cell count are difficult to interpret owing to the surgical interventions and the fact that the patients were given blood transfusions. However, one of the patients, Case 3, received only a single blood transfusion during the weeks immediately following the operation. In eighteen days, her red cell count fell by more than half from 3,500,000 immediately after the operation to 1,500,000. Total aplasia of the bone marrow would not be sufficient to explain such a fall because, even had this been the case, if the life of the erythrocytes had been of normal duration, the fall should have been slower. It is therefore necessary to assume an abnormally rapid destruction of the erythrocytes. It may be recalled that, in animals, the red blood count reaches a minimum two weeks after irradiation and that destruction of the red cells takes place; this is probably related to the hæmorrhages and especially to the passage of the red cells into the extravascular spaces where they are destroyed. (Waggener & Hunt 1958). It is possible that analogous phenomena take place in man.

Reticulocytes: The number of reticulocytes fell immediately after irradiation, and from the fifteenth day was less than 5%. The count began to rise again at the same time as the white blood count increased. At this stage, therefore, an increase in the number of reticulocytes is of no additional prognostic value to the changes in the red cell count.

Leucocytes: (*a*) *Lymphocytes:* In accordance with the classical picture, the number of lymphocytes fell rapidly three to five days after irradiation. The minimum was about 4% of the initial value – a figure similar to that observed in the rat after a dose of 400 rads. In 4 of the 5 patients, there was a slight rise in the lymphocyte count beginning on the eighth day and subsequently a renewed fall. The number of lymphocytes then remained at a very low figure, until about the twenty-second to twenty-fifth day. In Case 3 the lymphocyte count began to recover earlier and rose slowly until the twenty-fourth day (after the second irradiation) when a transitory fall appeared. The presence of infectious hepatitis may perhaps explain this unusual course.

As in the classical picture, the secondary appearance of abnormal lymphocytes was observed in these patients. Comparison of the lymphocyte levels in blood shows that they are very similar during the first three days in patients receiving 250 or 400 rads. The fall was only slightly more marked at twenty-four hours in the patient who received 600 rads.

(*b*) *Granulocytes:* The number of granulocytes began to fall almost immediately after irradiation; the fall was precipitate at first, but became slower after the fifth day. The granulocyte count then remained constant or even showed a slight tendency to rise. From the fifteenth day the number of granulocytes began to fall again, reaching a very low minimum from the eighteenth day in certain patients and from the eighteenth or twentieth day in others.[1] During this phase of almost total agranulocytosis, the white cell count was below 500, sometimes below 200. The phase lasted about seven days, the leucocytes beginning to increase again between the 22nd day (Case 1) and the 26th day (Case 2) after irradiation.

Platelets: The platelet count showed a regular fall after irradiation, beginning rather slowly. The number of platelets reached a minimum between the fifteenth and twentieth days in Case 1, between the twenty-second and twenty-eighth days in Case 2, between the seventeenth and twenty-third days in Case 3, and between the nineteenth and twenty-third days in Case 4. In each case, the minimum count was between 10,000 and 40,000 platelets per c.mm. In Case 5, the minimum count was reached a little earlier but the increase also began earlier.

Two of the patients (Cases 2 and 4) received transfusions of platelets, whereas the others did not. However, all patients showed comparable changes in the platelet count, in spite of this difference, and it is not possible to claim that the transfusions modified the number of circulating platelets. Comparable findings have been reported by Mathé *et al.* (1959) in leukæmic patients given radiation treatment. Since none of these patients showed any definite hæmorrhagic tendency or hæmorrhagic accidents, it is impossible to estimate the clinical value of the platelet transfusions, but *in vitro* they were found to have modified the plasma coagulation tests, in so far as the marked decrease in prothrombin consumption and prolongation of the bleeding time that accompanied the thrombopenia were corrected.

Mitotic index: The mitotic index was counted in the bone marrow of Case 5. Before irradiation it was already at a low level, a fact which may be due to the chronic renal disease.

After irradiation, the mitotic index did not change much during the first few days; at this time the cellularity of the bone marrow was nearly normal. During the secondary rise of granulocytes, ten days after the second irradiation, the mitotic index was higher reaching about twice the initial value; at this time, the cellu-

[1] In the two cases in which irradiation was performed in two sessions, the days are counted from the date of the second irradiation.

larity of the bone marrow was already poor. The most interesting fact is that one day before the beginning of the rise of the granulocyte count no mitosis was found among the 1,100 cells counted. Later, during regeneration a high mitotic index was found.[1]

Comparison of the hæmatological findings in accident victims and in our patients shows important differences. In 2 cases, the comparison is facilitated by the fact that the victims received about the same doses as our patients: Patient A of the Y-12 accident at Oak Ridge (Brucer 1958) was exposed to an estimated dose of 365 rads, and patient G of the accident at Vinca (Jammet *et al.* 1959) to a dose of approximately 400 rads, one-third being given by neutrons. The fall in the lymphocyte count began earlier and lasted longer in our irradiated patients: whereas the number of lymphocytes began to increase appreciably from the fifteenth day in the accident victims, there was no increase until later in the irradiated patients. Moreover, the lymphocyte counts in the accident victims never fell as low as those observed in our patients after irradiation.

The fall in the granulocyte count also began earlier, lasted longer and was much more severe in the patients who were deliberately irradiated. Conversely, the regeneration of the lymphocytes and recovery of the white cell count were more rapid in our patients than in the accident victims. This observation confirms that the more profound the fall in the granulocyte count the more rapidly does recovery take place and the higher is the figure reached on recovery.

Several facts may be taken into consideration to explain these differences. In the case of accident victims, the irradiation is never uniform; if a victim is estimated to have received a dose of 365 rads, for example, the variations in dose from one part of the body to another may reach 30%. Moreover, in contrast to irradiated patients, accident victims are exposed to a mixture of photons and neutrons. Finally, it is necessary to emphasize that accidental irradiation is of very brief duration – from a few microseconds to several seconds – whereas the deliberate irradiation of patients extends over several hours.

Hæmatological evolution after 600 rads: The hæmatological findings during the first two weeks after irradiation in the patient who received 600 rads were very similar to those of the patients who received 400 rads. The number of platelets fell to a lower level during the last days before death, but it must be pointed out that in this patient a post-operative thrombosis contraindicated platelet and fresh blood transfusions. Fever was very high in this patient but no pathogenic organism was discovered and during the autopsy no infection was found. No obvious cause of death was found. A fistula of the intestine was found on the eleventh day but no peritonitis was noted during the autopsy. There was purpura on the peritoneum and the pleura but no hæmorrhagic collection.

Fever: Two bouts of fever were observed in each of the patients. The first began on the day after the first irradiation, immediately after the operation; the second coincided with the phase of agranulocytosis.

The severity of the operation is not a sufficient explanation for the first fever peak, since other operations of comparable severity provoke only a slight febrile reaction. It must be emphasized that similar bouts of fever have not been observed in subjects accidentally exposed to irradiation nor in those of our patients who were submitted to a second irradiation several months after a transplantation of the kidney, without a subsequent operation.

The febrile peak coinciding with the phase of agranulocytosis, on the other hand, is observed in all irradiated subjects. The classical explanation is that it is due to infection, but in no instance could any pathogenic organisms be detected during this phase and no typical focus of infection was found. It should also be noted that antibiotics had no influence on the temperature.

Moreover, it is striking that in all the patients, a fall in the number of white blood cells was accompanied by a rise in temperature and, conversely, the temperature fell whenever the number of white blood cells increased. Unless the increase in the number of white blood cells leads to an instantaneous disappearance of the infection, it is necessary to reconsider the problem of the pathogenesis of the febrile reaction, as this does not appear to be solely related to the presence of an infectious process.

Infection and its Prevention

One of the facts that emerges from this study is that it is possible to diminish the risks of infection in irradiated patients. In fact, at no stage were the infections in our patients alarming and they never dominated the clinical picture. This is probably explained in part by the very rigorous aseptic precautions that were observed, the concentration of micro-organisms in the air of the room being reduced to less than 1% of that in the external atmosphere (Maisonnet 1960). The patient is kept in isolation for several weeks after irradiation in a room containing filtered air, delivered under pressure from an air-conditioning system and

[1]We wish to thank Dr H Jammet, Madame S Alibert and Dr N Parmentier, who allowed us to use data on the mitotic index which was counted in their laboratory

sterilized by exposure to ultraviolet rays. The patient's room communicates with a second room treated in a similar manner, where the nurses in charge of the patient are in constant attendance. This room communicates in turn with a semi-aseptic storage room in which the attendant physicians and nurses undress completely, disinfect their hands with alcohol, and put on sterile clothes and gloves before entering the sterile portion of the suite. Throughout the period of treatment, the medical and nursing staff are submitted to periodic swabbing of the nasopharynx and skin to ensure that they are not carriers of pathogenic organisms.

The flora of the air in the sterile rooms is controlled and the patient himself must submit to daily disinfection of the skin. The study of the microbial flora of the patient must start before irradiation. The organisms are identified, their pathogenicity studied and their sensitivity to antibiotics determined. In this way it is possible, even before irradiation, to carry out antibiotic treatment designed to eliminate pathogenic organisms from the patient's body.

On the other hand, the routine administration of antibiotics without knowledge of the infecting organisms does not appear to be satisfactory (Maisonnet 1960) and carries risks that are by no means negligible. It may lead to partial or total destruction of the normal saprophytic flora of the body and seriously disturb the microbial balance; this may facilitate the multiplication of certain borderline organisms, a result that may not be desirable in a person deprived of the natural defence mechanisms. There is also a risk of the multiplication of strains resistant to the antibiotics used. Furthermore, the disturbance in the microbial balance facilitates the development of mycotic infections, particularly those due to *Candida albicans*.

Finally, there is a risk that an incipient infection may be masked and that, under these conditions, it may become difficult to establish the clinical and bacteriological diagnosis necessary to carry out specific antibiotic therapy.

It is for these reasons that routine antibiotic therapy has been gradually abandoned in favour of the principle of withholding the administration of massive doses of antibiotics until after identification of the infecting organisms and determination of their antibiotic sensitivity.

The value of aseptic precautions is difficult to assess as we have not treated comparable patients without them, but it may be said in favour that we have never lost a patient from infection and it is possible that the absence of hæmorrhage is due to the precautions taken since experimental work has shown that bleeding occurs more often in infected animals.

Virus infection: One patient, Case 3, developed an infectious hepatitis twenty-two days after irradiation. There was a recurrence of the jaundice a few months later when the patient was irradiated. Jaundice has previously been reported in patients given bone marrow grafts (Mathé *et al.* 1959), and in the patient described by Merrill *et al.* (1960). Moreover, 2 patients presented a herpetic lesion of the corner of the mouth. Perhaps there may be some connexion between this observation and the frequency with which irradiated subjects exhibit herpetic infections – a finding reported by Ellis & Stoll (1949).

General Condition and Clinical Course

As in all heavily irradiated subjects, the clinical course in our patients showed four distinct phases: (1) A phase marked by mild digestive disorders and lasting for several hours after the completion of irradiation. (2) A latent period of variable duration. (3) A phase characterized by a profound change in the general condition and a rise in temperature; it coincides with the period of agranulocytosis and lasts about eight days. In Case 2, in whom the post-operative period was marked by several incidents (Küss, Legrain, Mathé, Nedey *et al.* 1960), there was a particularly severe deterioration during this phase. For this patient, owing to a new surgical procedure performed five days after the transplantation, the scar formation was not complete when agranulocytosis developed. During this phase the edges of the wound parted and the healing made no progress until the end of aplasia. The cessation of fever, the end of the period of bone marrow aplasia and the resumption of the scar formation were simultaneous. (4) At the end of phase 3, the patients entered a period of convalescence, during which they were euphoric and felt as though they had been resurrected. The body-weight increased very rapidly by several kilograms per week. Nevertheless, the patients remained tired and readily fatigued for several weeks.

Laboratory Studies

These are rendered difficult by the multiplicity of factors capable of bringing about biological changes and by the desire to avoid taking unduly large samples of blood.

Nitrogen metabolism: Indirect evidence regarding the changes in nitrogen metabolism can be obtained by examination of the curves showing the blood urea levels and the excretion of urea in the urine.

All patients at the end of agranulocytosis showed evidence of an increase in the quantity of nitrogen utilized for synthesis within the body.

α-amino nitrogen excretion in urine has been followed in Case 5. It is markedly increased. This

increase does not seem to be correlated only with the increase of the diuresis which occurs after the kidney homotransplantation. Furthermore there is also an increase in the number of amino acids found in urine. These two facts are similar to those already observed in the victims of the Yugoslav accident (Jammet *et al.* 1959).

Creatinuria is much increased and remains high until the third week after irradiation. This is in contrast to the results obtained at Oak Ridge (Brucer 1958) on the victims of the Y-12 accident, but corresponds well with animal findings and observations made on patients irradiated with higher doses.

Taurine urinary excretion was found to be elevated, the increase being greater than in the victims of the Y-12 accident. Four plasmatic enzymes (DNase, aldolase, SGOT, SGPT), also followed in Case 5, were lowered, especially during the third clinical phase.

Second Irradiation

Three and a half months after the first irradiation in Case 3, and two months after transplantation in Case 4, the changes in renal function prompted a second irradiation. In both cases, the technique used was similar to that described for the first irradiation, but the dose was only 100 rads to the centre of the body, delivered at a rate of 1·5 rad/minute. The effects of this second irradiation on the blood picture were of an intensity out of all proportion to the dose. In both patients it produced a severe and long-lasting bone marrow aplasia which began slightly later than in the case of the first irradiation. The white cell count remained below 500 per c.mm for more than nine days in Case 4 and at the same time the number of platelets fell to less than 30,000 per c.mm and the patient became anæmic. The evolution was even more dramatic for Case 3 who died fifty days after the second irradiation; this was the day after the end of the period of aplasia which had lasted for thirty-four days. Owing to the poor renal function, it had been necessary to remove this patient from the aseptic suite for detoxication with the artificial kidney. In spite of massive doses of antibiotics, septicæmia due to *Esch. coli* developed. This responded to further antibiotic treatment during the phase of agranulocytosis, but the patient died a few days later. The immediate cause of death was apparently a generalized infection with *Candida albicans*. The violence of these reactions shows that the hæmopoietic tissues had not yet returned to normal and were still suffering from the effects of the first irradiation. It should be noted in this connexion that a severe leucopenia (W.B.C. less than 600 per c.mm) also developed in Case 2 following treatment with small doses of nitrogen mustard four months after irradiation.

These are surprising findings that could not have been predicted from animal experiments, since it appears that in animals the effects of irradiation disappear almost entirely after a few weeks (Kohn & Kallman 1957, Rugh & Wolff 1957, Storer 1959, Baum & Alpen 1959, Tubiana & Frindel 1959, Baum 1960). Very few data are available on man. However, Miller *et al.* (1958) suggested that the effect of a second total body irradiation might be greater than the effect of the first one.

Was the reaction of our patients to the second irradiation due to the fact that the hæmopoietic stem cells still carried lesions produced by the first irradiation which increased their sensitivity to radiation? Such an explanation is not very likely, since it is difficult to see what the nature of these lesions could be. Alternatively, one might assume that in these patients hæmopoiesis is maintained by a greatly reduced number of stem cells dividing very rapidly; the increase in the hæmatological effect might then be a consequence of the small number of stem cells.

For the second irradiation (100 rads) to reduce the number of stem cells to a figure comparable to the level after the first, it would be necessary for the number present at the time of the second irradiation to be only 10–15% of the number possessed before the first irradiation. Such a hypothesis does not appear improbable, since it is known that in extreme circumstances – for example, after severe hæmorrhage – bone marrow production may increase up to eight times; but still it would not explain why regeneration is so slow.

The severity of these reactions caused by the second irradiation provides one more illustration of how cautious one has to be in extrapolating to man the findings in experimental animals.

Conclusions

Uniform whole-body exposure to doses of 400–450 rads appears to be well tolerated by man, provided that certain precautions are observed. With such doses, hæmorrhages are of a relatively minor nature and easy to control. The risk of infection is much more serious; it would appear that this danger can be averted by observing strict aseptic precautions and that it is possible for a patient to live for a month or more in an atmosphere much more sterile than that of an operating theatre. Under these conditions and by the use of antibiotics, not as a routine measure, but for specific therapy, it appears possible to reduce the risks of infection.

It is obviously difficult to make comparisons between human beings living under such conditions and laboratory animals since whole teams

of doctors and bacteriologists would be required in order to keep a control on a few animals. The extrapolation to man of animal findings in regard to the determination of the LD_{50} – a risky procedure in any case – thus becomes still more open to criticism.

A second irradiation performed several months after the first produces effects of surprising intensity. Whatever the reason for this may be, it gives emphasis to the above warning.

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The Outlook for Transplantation of the Kidney in Man

by Professor M F A Woodruff FRCS (*Edinburgh*)

It has been said that some 250,000 people die each year as a result of renal insufficiency. It is impossible to estimate how many of these lives could be saved if the problems which at present limit the use of renal transplants were all solved, but the number is certainly considerable. These problems are of four kinds: (1) Technical, (2) immunological, (3) storage, and (4) ethical and legal.

Technical Problems

The technical problem of renal transplantation has largely been solved. The blood supply to the transplant must be re-established reasonably quickly – preferably within an hour unless special precautions are taken – and provision made for the drainage and collection of urine. In practice this is best achieved by placing the transplant in an extraperitoneal position in the iliac fossa (the donor's left kidney in the recipient's right iliac fossa or *vice versa*). The usual procedure is to anastomose the artery of the transplant end-to-end to the divided internal iliac artery of the recipient, and the vein of the transplant end-to-side to the external iliac vein of the recipient, but it is equally satisfactory to make both anastomoses end-to-side to the external iliac artery and vein respectively. Difficulty may be encountered if the transplant has two arteries, or if the recipient's arteries are atherosclerotic but, as Woodruff *et al.* (1961) have reported, it may still be possible to make a successful transplant. The ureter of the transplant may be anastomosed to the bladder or to the distal part of the ureter of the recipient. In either case it is desirable to sacrifice the distal two-thirds of the ureter of the transplant, because this not only reduces the risk of ischæmic necrosis of the distal part of the ureter but also, as Murnaghan (1960) has suggested, probably reduces the risk of reflux.

Transplantation of a kidney necessarily implies complete interruption of the nerve supply, but fortunately this does not seem to matter; thus a transplant may maintain life even if both the recipient's kidneys are removed at the time of (or just before) the transplantation, and within a few weeks its functional efficiency may be as good as that of a normal kidney.

This is illustrated by cases in which a kidney has been transplanted from a healthy identical

twin, for in this event the immunological problem does not arise. Most of these cases have been reported by Murray and his colleagues in Boston (Murray *et al.* 1958). My own experience is limited to a single case (Woodruff *et al.* 1961). This has been fully reported elsewhere.

In summary, however, it may be said that the transplant shows normal clearance of creatinine and para-amino hippuric acid, and yields a normal intravenous pyelogram. It conserves sodium under conditions of sodium depletion, and is able to play its part in the regulation of acid-base equilibrium. Since the operation the recipient's blood urea nitrogen and blood pressure have fallen to normal, his retinal exudates and hæmorrhages have disappeared, and he has returned to work.

The Immunological Problem

It is now common knowledge that homografts as a general rule evoke a state of immunity in consequence of which they are destroyed within a few days or weeks. As evidence for this we may cite the fact, discovered by Gibson & Medawar (1943) and since confirmed by many observers, that a second graft from the same donor to the same recipient is normally destroyed more rapidly than the first, and the discovery of Mitchison (1954) that the state of increased reactivity induced by a homograft can, under certain conditions, be transferred passively by means of cells to a third party.

Some grafts used in surgery, such as massive bone grafts and segments of blood vessels, may be functionally effective even though they do not survive, because they provide a scaffolding for regenerating recipient tissues, but obviously this is not relevant to the subject of organ transplantation. There are, however, exceptions to the rule that homografts are rapidly destroyed, and these may be arranged under the following headings: (1) Compatibility of donor and recipient. (2) Special properties of certain tissues, notably cornea and cartilage. (3) Special properties of certain sites, notably the brain and the anterior chamber of the eye. (4) Constitutional abnormalities of the recipient, notably uræmia, agammaglobulinæmia, Hodgkin's disease, and pregnancy. (5) Experimental and therapeutic procedures.

I shall consider only the question of donor-recipient compatibility, and four experimental and therapeutic procedures, namely, (*a*) administration of corticosteroids or ACTH; (*b*) induction of specific immunological tolerance; (*c*) whole body irradiation; and (*d*) administration of cytotoxic drugs.

Compatibility of donor and recipient: Complete compatibility occurs when the donor and recipient are identical twins, and virtually complete compatibility between members of the same sex can be achieved in experimental animals by brother-sister mating over many generations. Non-identical human twins may show a fairly high degree of compatibility, which is sometimes, as in the cases reported by Hamburger *et al.* (1959) and Merrill *et al.* (1960), sufficient to permit successful renal transplantation after a dose of irradiation which would otherwise probably have been insufficient. Complete compatibility between non-identical twins is, however, extremely unlikely except in the rare case when they happen to be blood chimeras (*see* Woodruff & Lennox 1959).

It is important to note that, as Woodruff & Allan (1953) have reported, compatibility in respect of a large number of red cell antigens is not a sufficient condition (though it may well be necessary) for tissue compatibility in general.

Administration of corticosteroids or ACTH: It is possible to double or treble the period of survival of various types of homograft by the administration of corticosteroids or ACTH (for review *see* Woodruff 1960, p 104 *et seq.*). The effect varies in different species; administration of these substances is being tried clinically in combination with other procedures such as whole body irradiation. Their value, however, is still *sub judice*.

Induction of specific tolerance: The discovery of immunological tolerance by Medawar and his colleagues (Billingham *et al.* 1953, 1955, 1956) provided a solution of the immunological homograft problem at an experimental level. Briefly they showed that if a mouse embryo *in utero* was injected with living cells from a mouse of a different strain it would under certain conditions, when it grew up, accept permanently grafts of skin from the original cell donor (or another animal of the same genetic constitution). It was shown subsequently in rats (Woodruff & Simpson 1955), mice (Billingham & Brent 1957*a*) and other species that tolerance could also be induced for a short time after birth, and an attempt was therefore made to induce tolerance to the tissues of the father in two human infants (Woodruff 1957). Some degree of tolerance was in fact achieved, but these investigations were abandoned when it was discovered by Billingham & Brent (1957*b*) that immature animals injected with foreign cells sometimes developed a condition which they called *runt disease*, characterized by diarrhœa and wasting, and often culminating in death. This phenomenon occurs only when the injected cells are able to react immunologically against the recipient, and is an example of what is now termed *graft-versus-host disease*.

There are grounds for believing that tolerance might be induced in adults simply by using a very

much larger dose of foreign cells, but it seems doubtful whether enough viable cells could be obtained from one donor to achieve this in man. There are, however, two other possibilities. One is to combine the injection of donor cells in feasible dosage with whole body irradiation or administration of cytotoxic drugs. The other is to inject preparations of the transplantation antigens derived from donor tissues. In this way a much wider range of tissues could be utilized, and the risk of graft-versus-host disease could probably be completely eliminated.

Whole-body irradiation: It has been known for nearly half a century, from the work of Hektoen and Murphy, that irradiation with X-rays may impair an animal's capacity to react immunologically to bacterial antigens, heterologous erythrocytes and transplanted tumours. It seemed likely therefore that the survival of homografts of normal tissues could be prolonged by irradiating the recipient prior to transplantation. Proof of this was provided by Dempster *et al.* (1950), who showed that skin homografts in rabbits given 250 rads whole body irradiation survived longer than in non-irradiated controls, but the longest survival was only twenty-four days.

Immunologically, it is probably easier to obtain long survival of homotransplants of whole organs by vascular anastomosis than of free homotransplants of skin, and probably also easier to obtain long-surviving organ transplants in man than, for example, in dogs. Moreover, and this is significant in relation to transplantation of the kidney, survival of a homotransplant is facilitated if the recipient is uræmic. In consequence human renal transplants have been observed to function for several weeks, and in one instance for 176 days (Hume *et al.* 1955), in patients not subjected to any special treatment. Even more striking results have been obtained in patients given 400–600 rads whole body irradiation. In two of these, as Dr Tubiana has mentioned, the donor and recipient were non-identical twins, but Küss and his colleagues (Küss, Legrain, Mathé, Nedey *et al.* 1960: Küss, Legrain, Mathé & Nedey 1960) have reported one case in which a kidney transplanted from a girl to her non-twin brother continued to function until the patient died four months later from metastatic cancer, and another patient treated by Küss *et al.* (1961), who received a kidney from her brother-in-law in June 1960, is still alive.

There have, unfortunately, been many failures, only some of which have so far been reported. They appear to have been due in the main either to death of the patient from infection or hæmorrhage, or to rejection of the transplant.

The risk of infection can be reduced by maintaining the patient under conditions of the strictest possible asepsis, and if infection does occur the chance of retrieving the position will depend on whether specific antibiotic therapy is available and if so how promptly it is begun.

Hæmorrhage is a grave danger if the patient becomes grossly thrombocytopenic, and it is therefore essential to give repeated transfusions of blood platelets or fresh blood. Since the blood will in general not come from the graft donor it is advisable to avoid including viable leucocytes, and experiments are in progress (Davis, Nolan & Woodruff, unpublished data) to determine whether leucocytes can be destroyed without damaging platelets by irradiating the blood.

It seems likely that the risk of graft rejection would be reduced if the dosage of irradiation could be increased, and the discovery that animals may recover after otherwise lethal irradiation if given transplants of hæmopoietic tissue, by intravenous infusion or otherwise (Lorenz *et al.* 1951, *see* Woodruff 1960 for review) suggests that better results might be obtained by giving larger doses of irradiation than in the cases so far described, followed by transplantation of bone marrow and also of a kidney from the same donor. Unfortunately, such a procedure involves very serious risks.

In the first place, while it has been shown that foreign marrow transplanted to heavily irradiated animals may survive indefinitely (in which event the animals are termed *radiation chimeras*), this has been reported only once in man (Beilby *et al.* 1960) and the development of chimerism may have been due partly to the fact that the patient was suffering from Hodgkin's disease and received an alkylating agent as well as irradiation.

Secondly, even if the transplantation of marrow does prevent or correct the severe marrow aplasia which would otherwise result from the irradiation it does little to protect the gut and other tissues.

Thirdly, unless the donor is an identical twin (in which case irradiation would be unnecessary) there is a danger that the recipient, after an initial period of recovery, will develop serious and possibly fatal *secondary disease*. The symptoms of this condition, which was first described by Barnes *et al.* (1956), closely resemble those of runt disease (*vide supra*), and it is now clear that secondary disease, too, is due to some of the grafted cells, or their descendants, reacting immunologically against the recipient.

In mice the severity of secondary disease depends *inter alia* on the strain combinations employed, and the nature and number of the cells injected. The magnitude of the hazard after transplantation of bone marrow in man is still uncertain, but Mathé *et al.* (1960) have adduced evidence which suggests that it is considerable.

Secondary disease would probably not occur if fœtal hæmopoietic tissue could be used instead of adult, but although fœtal liver has been used in a number of human patients after irradiation, there is still no convincing evidence that it can provide adequate hæmopoietic replacement.

If chimerism could safely be induced in patients it would clearly be a great step forward because it would be possible to refrain from hazarding the donor's kidney until this had been done.

Administration of cytotoxic drugs: Goodwin (personal communication) administered nitrogen mustard to a patient who had received a kidney transplant. The patient died five months later from respiratory infection, but the transplant was still functioning.

Calne (1960, 1961) has succeeded in prolonging the survival of kidney transplants in dogs by administering an antimetabolite, 6-mercaptopurine, and this drug is also being tried clinically though so far no reports have been published.

Clearly both the alkylating agents and the antimetabolites involve dangers comparable to those of whole body irradiation. Whether any of these drugs, either alone or in combination with irradiation, can achieve the desired result without causing serious damage remains to be seen.

It is apparent that advance in the clinical field depends on progress in the laboratory, and in particular on an increase in our understanding of, and control over, the immunological processes concerned in homograft rejection. As Voisin (1958) has expressed it: 'C'est dans la domaine immunologique que se jouera, que se joue déjà, la partie passionnante dontl 'enjeu est la possibilité de pratiquer des homotransplantations d'organes vitaux assurés d'une survie définitive.' But if the immunologist has the major role, the radiotherapist and surgeon have an important contribution to make, for we can provide essential techniques unfamiliar to most biologists, and it is our task to apply in the clinic the discoveries of the laboratory.

The Problem of Storage

Attempts are being made to store whole kidneys by cooling, by continuous perfusion, or by a combination of these methods, but so far the period for which a kidney can be maintained in a satisfactory state for transplantation is a matter of hours.

Ethical and Legal Problems

The Tissue Grafting Act will make it possible, under certain conditions, to obtain any type of tissue or organ from a cadaver for purposes of transplantation, and not merely cornea as hitherto. Unfortunately if a kidney is to be used as a transplant it must be obtained within minutes of death, and this is only occasionally possible.

In consequence one must still look to living volunteers, and this raises difficult ethical (and one suspects also legal) problems.

As far as the ethical situation is concerned, if the patient's only hope of survival lies in transplantation and he is lucky enough to have a healthy identical twin with two normal kidneys, it seems right to put the facts to the twin, and accept a graft if offered. In the absence of an identical twin the situation is much more difficult, because the prospects of success are small but not entirely negligible. Our colleagues in France and the United States have shown us how to face these agonizing decisions with compassion and with courage. In trying to follow their lead we may perhaps gain some comfort from the reflection that:

> '. . . diseases desperate grown
> By desperate appliance are reliev'd
> Or not at all.'
>
> (*Hamlet*, IV, iii.)

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(Organizacion mundial de la salud serie de monografías, no. 45)
pp 88 17s 6d

Book reviews

A Short History of Clinical Pathology
by W D Foster MD
pp xi+154 illustrated 27s 6d
Edinburgh and London: E & S Livingstone 1961

It is particularly apt, at the time when pathologists in this country are actively debating the future organization of pathology, that a book should appear on the history of clinical pathology. Previously books have been written on the history of pathology, but none on clinical pathology which is mainly concerned with the application of laboratory techniques to the diagnosis of disease and the control of certain forms of treatment.

After a brief introduction to the origin of clinical pathology Dr Foster gives short accounts of the development of its four main branches of morbid anatomy, chemical pathology, bacteriology and hæmatology. These chapters relate the progressive application of various laboratory methods to the solution of everyday clinical problems. There follows a chapter entitled 'Clinical laboratories' which describes the provision of laboratory facilities and the difficulties of the pioneer clinical pathologists in this country.

The final chapter on 'Organization of clinical pathology to the present day' is contributed by Dr S C Dyke. It is particularly interesting and revealing and tells of the struggles of the early clinical pathologists to establish their specialty. It describes the formation of the Association of Clinical Pathologists and ends with a provocative section on the future organization of pathology.

Strangulation Obstruction
by Isidore Cohn Jr MD DSC(Med)
pp xxii+273 illustrated 94s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

The mechanism by which strangulation of bowel causes death has for long been obscure. Professor Cohn in his monograph has gone a long way towards clarifying this most important problem. He has used standardized techniques for producing strangulation in dogs and, step by step, has been able to isolate the essential factors which cause death. It is confirmed that bacterial proliferation plays a most important role and that sterilization of strangulated gut by antibiotics placed within the lumen of the bowel will allow revascularization and recovery in many cases. Some toxic product of bacteria, especially clostridia, is responsible for death. Presumably the next step will be to identify the nature of this toxin and its pharmacological action. The considerable literature on this subject is critically reviewed and it is a measure of the author's work that of 367 references listed, 35 bear Professor Cohn's name.

International Review of Tropical Medicine Vol 1
edited by David Richard Lincicome
pp xii+300 illustrated 80s
New York and London: Academic Press 1961

This is a new publication and the intention is to issue it annually. The enormous amount of medical literature being produced renders it necessary for very strong reasons to be brought forward to justify yet another publication. The reasons given in the preface emphasize the need for more study of tropical medicine. It is for example, stated that 'the problems of health are international' and the world is 'time-shrunken'; attention needs to be focused on tropical areas of the earth because 'the frontiers of the practice of science and of medicine' are there. A heterogeneous collection of papers such as are here presented may well assist in furthering studies in this field but the arguments supporting this point are not clearly brought out and one wonders whether more systematic selection of papers into groups of related subjects would not be better.

The papers in this volume are all valuable individually and include an excellent review by Dr Charles Wilcocks on sources of information on tropical medicine. He concludes with a consideration of the form and style in which scientific papers should be presented and authors of many other papers – not excluding some of those in this publication – could with advantage take note of his precepts.

There is a very helpful paper by Dr R G Cochrane on the present position in leprosy and here he clarifies many of the confusing trends in leprosy and presents his own very authoritative interpretation of modern practice. There are other papers on *Entamœba histolytica* infection, xerophthalmia, immunochemical staining with fluorescent antibody, ticks and tick-borne diseases and a historical study of Patrick Manson as a parasitologist.

The Adrenal Cortex
The Proceedings of a Symposium organized by the Association of Clinical Pathologists held in London October 14–15 1960
edited by G K McGowan and M Sandler
pp xii+226 illustrated 25s
London: Pitman 1961

This Symposium was specifically designed to have an educational function rather than to be a discussion between experts, and it is introduced as such in a lucid preface by the Chairman, Professor C H Gray. It can be said to succeed in the case of those papers which fulfil this purpose of the Symposium, but a few of the papers show a

regrettable tendency to chauvinism, which, while perhaps excusable on the grounds of protective mimicry after ten years of such behaviour in the clinical and paraclinical literature of the U.S.A. and U.S.S.R., is quite out of place in an educational discourse. It is strange that no references are offered in the paper on aldosteronism; that there appears to be no reference to the work of G W Thorn and his colleagues in the whole of the clinical section; and that there is only one reference to the work of Gallagher and his group on normal and pathological steroid metabolism in man. While the papers of the clinical section are on the whole clear and useful summaries of present knowledge, the clinical pathologist who desires a fuller and more balanced account of adrenocortical hyper- and hypo-function would be well advised to supplement some of them with further reading. Why, for instance, in the paper on the complications of therapy with corticosteroids is there no mention of the work of the M.R.C. Panels on the use of cortisone and other similar agents in rheumatoid arthritis, in the nephrotic syndrome, and in rheumatic fever; or of the excellent studies of Savage and his group on the differences between therapy with cortisone and with ACTH?

Most of the papers in the section on chemical pathology are admirable introductions to this difficult field and succeed in being both up to date and easily understandable. Outstanding among these are the papers by Norymberski on his methods of estimating specific subgroups of the metabolites of the adrenocortical hormones, and of Brooks on the use of paper chromatography in estimating steroids in human urine which is probably the best summary of both the general principles and the important practical details that the newcomer to the field can hope to read.

Another valuable paper in this section is that by Professor Patterson. The organizers of this Symposium are to be congratulated in having managed to remove the bushel that has for too long obscured this steadily glowing candle. Those who have been troubled by difficulties in trying to repeat some of the published methods will find this paper extremely helpful reading.

The Day Hospital Movement in Great Britain
by James Farndale BCOM FHA MRSH
pp xvii+430 illustrated 84s
London: Pergamon Press 1961

'Day hospital' is a term which is becoming increasingly familiar, now that so many patients are being treated in their home environment. However, before Mr Farndale published this book, few people can have had the opportunity of studying more than one or two of these new units. Here for the first time it is possible, in one book, to learn about many more, from the clear and detailed descriptions of the 65 day hospitals and day centres which the author visited in 1958/59. He shows how they have been emerging as separate, experimental units, particularly for the treatment of psychiatric and geriatric patients. The variety of organization of these day hospitals and centres makes interesting reading, especially for those concerned in undertaking similar projects.

The book is divided into two parts. The first covers the background of the day hospital movement, psychiatric and geriatric day hospitals, medical and industrial rehabilitation day centres and welfare centres. In the second part there are detailed accounts of each of the day hospitals and centres.

Although, as the author foresaw, the material is already becoming out of date, the book is, especially from the administrative angle, an admirable history of and comment on the 'day hospital movement'.

Some Aspects of Obliterative Vascular Disease of the Lower Limb
by J A Gillespie MD ChM FRCS
and D M Douglas ChM FRCS
pp vii+136 illustrated 30s
Edinburgh and London: E & S Livingstone 1961

The treatment of peripheral vascular disease is at present based on many unproven hypotheses some of which the authors of this book have tested scientifically. The value of sympathectomy, the place of vasodilators and the causes of return of sympathetic function after denervation have been carefully evaluated by plethysmography and measurement of skin temperature and conductivity. The authors have shown how permanent are the effects of sympathetic denervation in the lower limb, how little vasodilators can help and how sympathetic activity can return either by the development of intermediate nerve pathways or by nerve sprouting. Anyone who has to treat peripheral vascular disease either medically or surgically should read this book. Its value would be greatly increased if, in a future edition, the chapters on pathology, methods of investigation and direct arterial surgery could be expanded.

Physiology of the Salivary Glands
by A S V Burgen MD MRCP and N G Emmelin MD
pp vii+279 illustrated 35s
London: Edward Arnold 1961

Here is an authoritative, critical and up-to-date account of a field which was once popular but is nowadays rather neglected. Anatomical, physiological, biochemical and biophysical aspects of mammalian salivary secretion are dealt with in 14 chapters and the work carried out by the authors on cats and dogs during the past ten years repre-

sents the framework or major part of most chapters. Each chapter is more or less self-contained and the coverage of the literature is extensive. The text is a masterpiece of clarity and on the whole the authors have succeeded in avoiding confusion arising from species variations and from differences between individual glands. Those interested in the mechanisms involved in secretory processes will find Chapter 12 particularly attractive.

No medical library should be without this beautifully produced monograph which is likely to become a standard reference book on the subject.

The Metabolism of Cardiac Glycosides
by S E Wright PHD MSC ARIC
American Lecture Series No. 368
pp viii+86 illustrated 38s
Oxford: Blackwell Scientific Publications 1960

The topics discussed in this book are the chemical nature of cardiac glycosides, the relation between their molecular structure and pharmacological activity, methods for analysis in urine and animal tissues, and their metabolism, absorption, distribution in tissues and excretion. Work in this field has been helped by the incorporation of radioactive isotopes into the compounds and by the use of recently developed sensitive biological assay methods using the embryonic chick or duck hearts. Most of the information deals with metabolism of cardiac glycosides in animals; there is disappointingly little about metabolism in man. The most important general statement is that, contrary to older teaching, there is no evidence that cardiac glycosides have a specific affinity for heart muscle.

There are 74 pages of text and 171 references to the literature. The price, 38s, is excessive for such a small book.

Dermatology for Students
edited by Ray O Noojin MD
pp xiii+301 illustrated 76s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

This book, as the title implies, has been written for the medical student and undoubtedly fulfils a need. It does not set out to cover the whole of dermatology, but deals with thirty of the most common skin conditions met with in practice. No fewer than 28 dermatologists from different parts of the United States contribute to the various chapters.

After an introductory chapter on the anatomy and physiology of the skin the various dermatoses are considered in a clear and concise manner. The text is illustrated by a large number of high-class black and white photographs and, in addition, there is a useful colour atlas of 28 plates.

In this otherwise excellent book a few points require comment. For instance, in the first chapter few would agree with the view that nerve fibres are not found in the epidermis, nor with the statement that lichen planus does not involve the nails. In general, therapy follows conventional lines but there is no mention of dithranol in psoriasis or formalin for warts, whereas 10% sulphacetamide lotion is advocated for secondarily infected seborrhœic dermatitis. In the chapter on pityriasis rosea the page headings bear the title of lichen planus – a printing error which can easily be corrected in subsequent editions.

Finally, it is a pity that scabies and pediculosis received no mention.

Apart from these minor criticisms this book achieves its aims and can be confidently recommended to the student.

The Air We Breathe:
A Study of Man and His Environment
edited by Seymour M Farber MD
and Roger H L Wilson MD
pp xv+414 illustrated £5 12s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

This book reports proceedings of a symposium held in San Francisco in 1960 and presents both the major communications and records of panel discussions. It has a remarkably wide coverage. The first section on 'The Normal Atmosphere and its Variation' comprises interesting accounts of past and present views on the composition of the atmosphere of our planet with speculations on the composition of the atmosphere of other planets in the solar system. Reviews follow of the reactions of the human organism to changes in climatic stress, particularly temperature, and of physiological changes at altitude and at depth under the sea.

The second main section is concerned with air pollution in industry and contains accounts of dust retention in the lungs by Hatch, of the effects of chemical irritants by Mancuso and of the radioactive pollution of the atmosphere by nuclear explosions and the atomic energy industry by Newell. The next section on 'urban living' contains four papers which deal with air pollution in towns, both acute and chronic, their effects on producing disease and the means by which they may be prevented. There is an interesting contrast here between the straightforward British approach to this problem presented by Lawther and the rather more elaborate American approach presented by Prindle and Chambers.

The last two sections in this book are concerned with specific disease problems. Professor Gough reviews the pathological effects of dusts in the lungs. Recent studies of the immediate effects

of various inhaled aerosols including tobacco smoke on pulmonary function are presented by McIlroy and Nadel. The possibility that negative ions may be of some therapeutic value is presented by Yaglou. The final section is concerned with the ætiology of lung cancer. It is valuable to have the views of Kotin, Hammond and Berkson on the tobacco-smoking problem presented in juxtaposition.

This book will provide an admirable source of reference for clinicians, epidemiologists and public health officers in relation to many of the effects of the environment in which we live upon the health of civilized communities to-day. The discussions are well reported and add considerably to the formal papers.

Regional Neurochemistry: The regional chemistry, physiology and pharmacology of the nervous system
Proceedings of the Fourth International Neurochemical Symposium, Varenna, Italy, June 1960
edited by S S Kety and J Elkes
pp xvi+540 illustrated 84s
Oxford: Pergamon Press 1961

Within the limitation of the complex character of the cerebral organization the approach of regional histo- and cyto-chemistry is extremely useful. The emphasis accorded to the relationship between structure and function at this level is the main strength of this volume.

Three main trends in neurochemical research are represented. First, the location of biochemically important constituents and reactions in the subcellular particles, e.g, the regional distribution and subcellular localization of enzymes; formation, distribution and metabolism of substrates, nucleic acids and tracer metals; morphological basis of neurosecretion and binding of neurohormones.

The second approach is by the study of chemical and metabolic differences in the different parts of the brain.

The third route of study is to recognize the chemical differences between different layers and cell types of the cortex and in some specialized parts of the central nervous system, e.g. neurohormonal function of pituitary and hypothalamus, sensitivity of different areas to hormonal stimulation.

The symposium incorporates pharmacological studies such as the effect of neurotrophic drugs on the different parts of the nervous system, works on various amines, localization of the action of convulsants, and many others.

The book contains 47 papers covering the main current trends in neurochemistry and is therefore invaluable to all interested in this field.

The Chemistry of Brain Metabolism in Health and Disease
by J H Quastel PhD DSc FRCS
and David M J Quastel MD CM
pp xi+170 52s
Springfield, Ill.: Charles C Thomas
Oxford: Blackwell Scientific Publications 1961

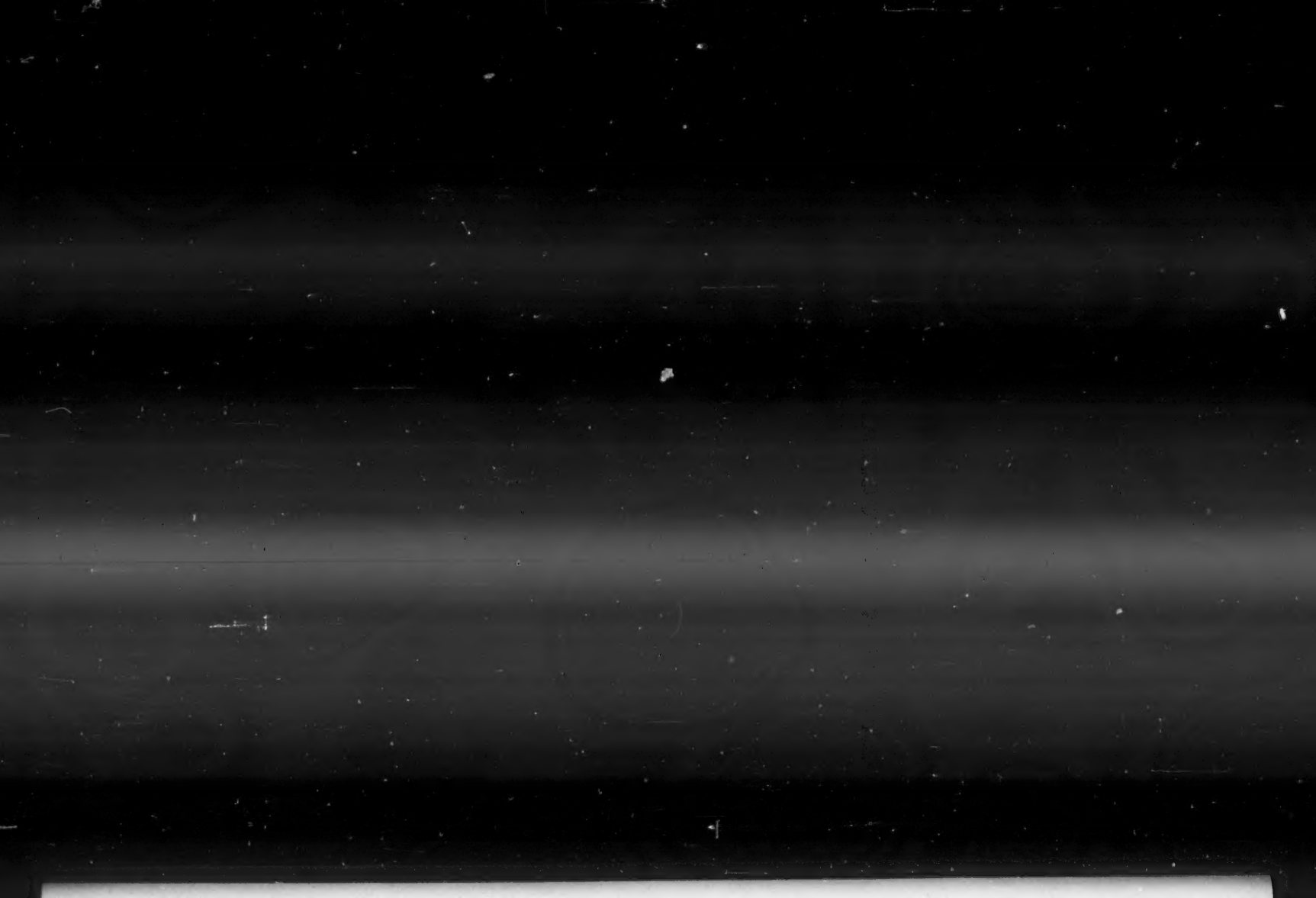
Can the chemistry of metabolism of one organ of the body offer a suitable subject for a book? The present account would suggest not, with respect to the brain, though readers will gain much information about the general biochemistry of neural systems. The text is relatively short (120 pp) and yet a minority would appear to be concerned with the chemistry of brain metabolism, and much with other aspects of metabolism, with transport or with modification of metabolism under different physiological and pathological conditions; the chemistry of cerebral constituents, independently of their metabolism, also rightly receives attention.

It is indeed very necessary in describing a metabolic process to indicate not only its chemistry but also its speed and the system in which it is studied. Here the authors' use of the word *brain* to mean at different times either the intact organ *in situ*, or preparations variously derived from it, may lead to confusion. 'Tartronic acid inhibits brain respiration . . .' is found only by referring to the original paper, to describe a study of slices of cerebral cortex *in vitro*. Also, when several references are consulted, the hydrogen carrier enzymes in 'the cell', referred to under *Steroids* and mediating between the nicotinamide nucleotides, are found to have been characterized in yeasts, in plant tissues and in the liver, kidney and placenta rather than in the brain. The text does not indicate this; much of the book is thus appropriate to those who can consult and appraise its valuably numerous references.

The Editor's foreword is distasteful and it is regrettable that the work of Professor Quastel, who has made notable contributions to the book's subject, should be placed in the setting of 'Our Living Chemistry Series'.

Physiology for Nurses
(Modern Nursing Series)
by Deryck Taverner MBE MD FRCP
pp ix+236 illustrated 12s 6d
London: English Universities Press 1961

The author is to be warmly congratulated on having achieved his object 'to give to nurses a clear, concise and accurate account of human physiology'. The book is written in simple language and is easy to read, yet there is a wealth of scientific knowledge in this small volume. The text is well illustrated by original, clear and dramatic diagrams. The intelligent student will appreciate the application of physiological principles to the care of patients in the wards.



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Brit. med. J., 1960. 2, 138

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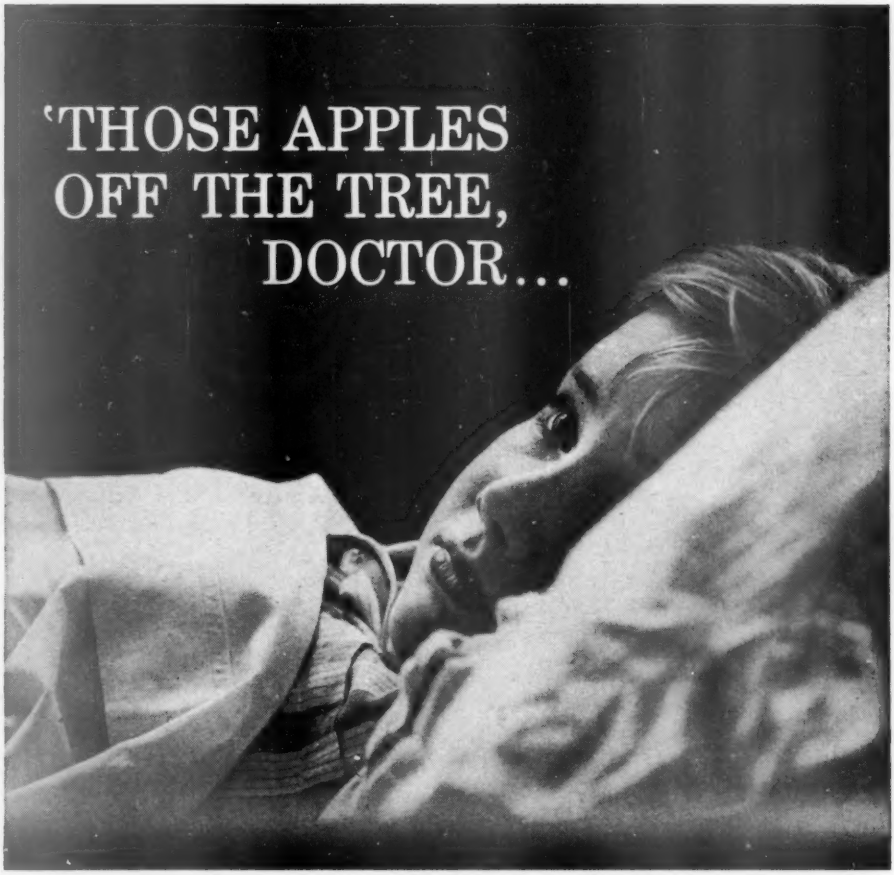

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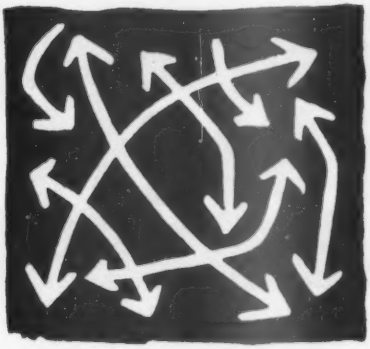

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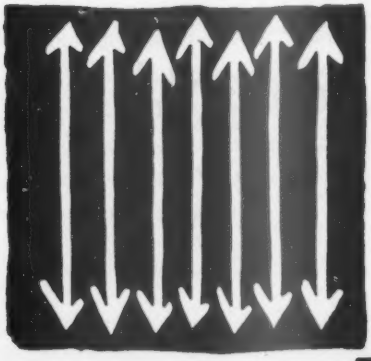

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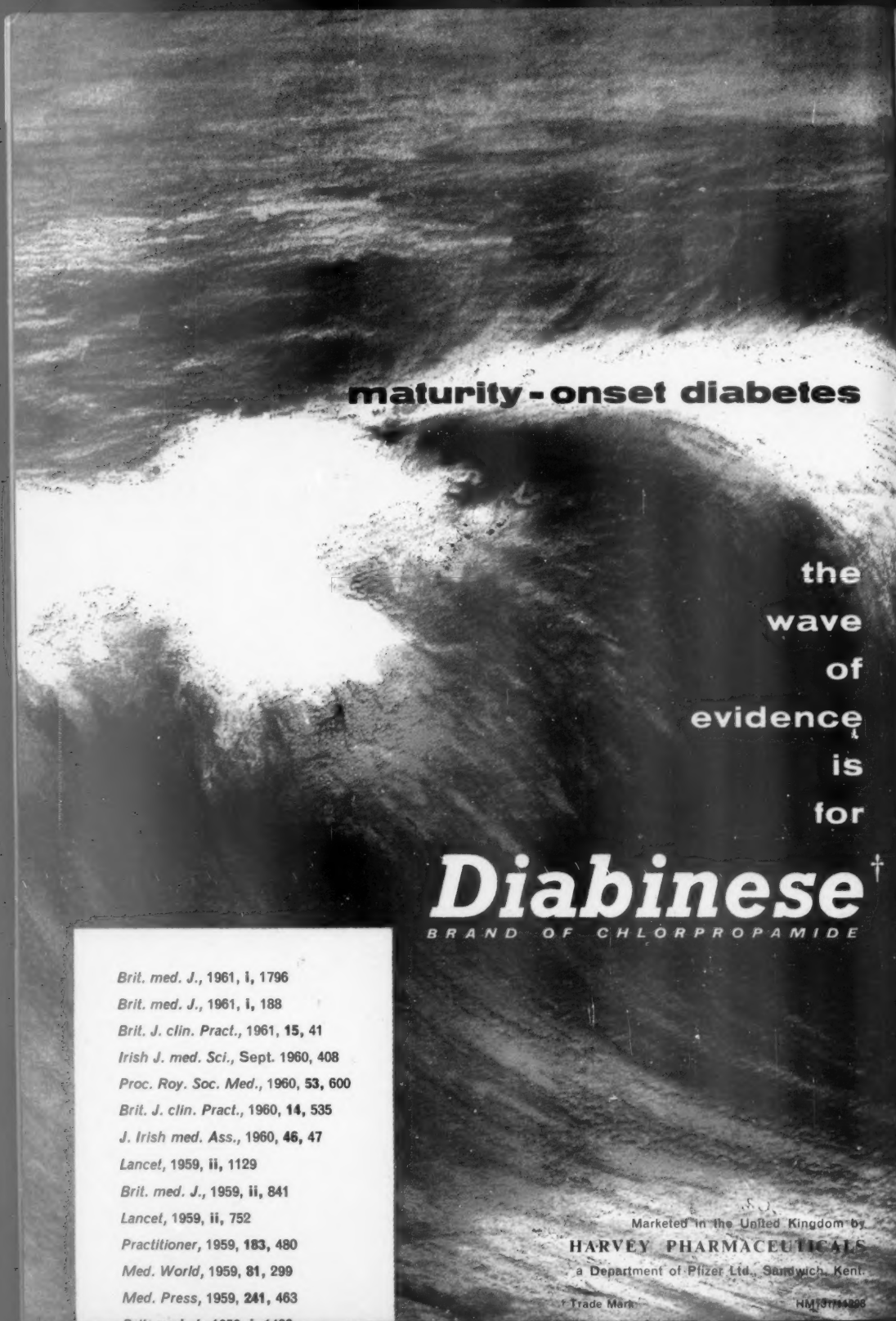
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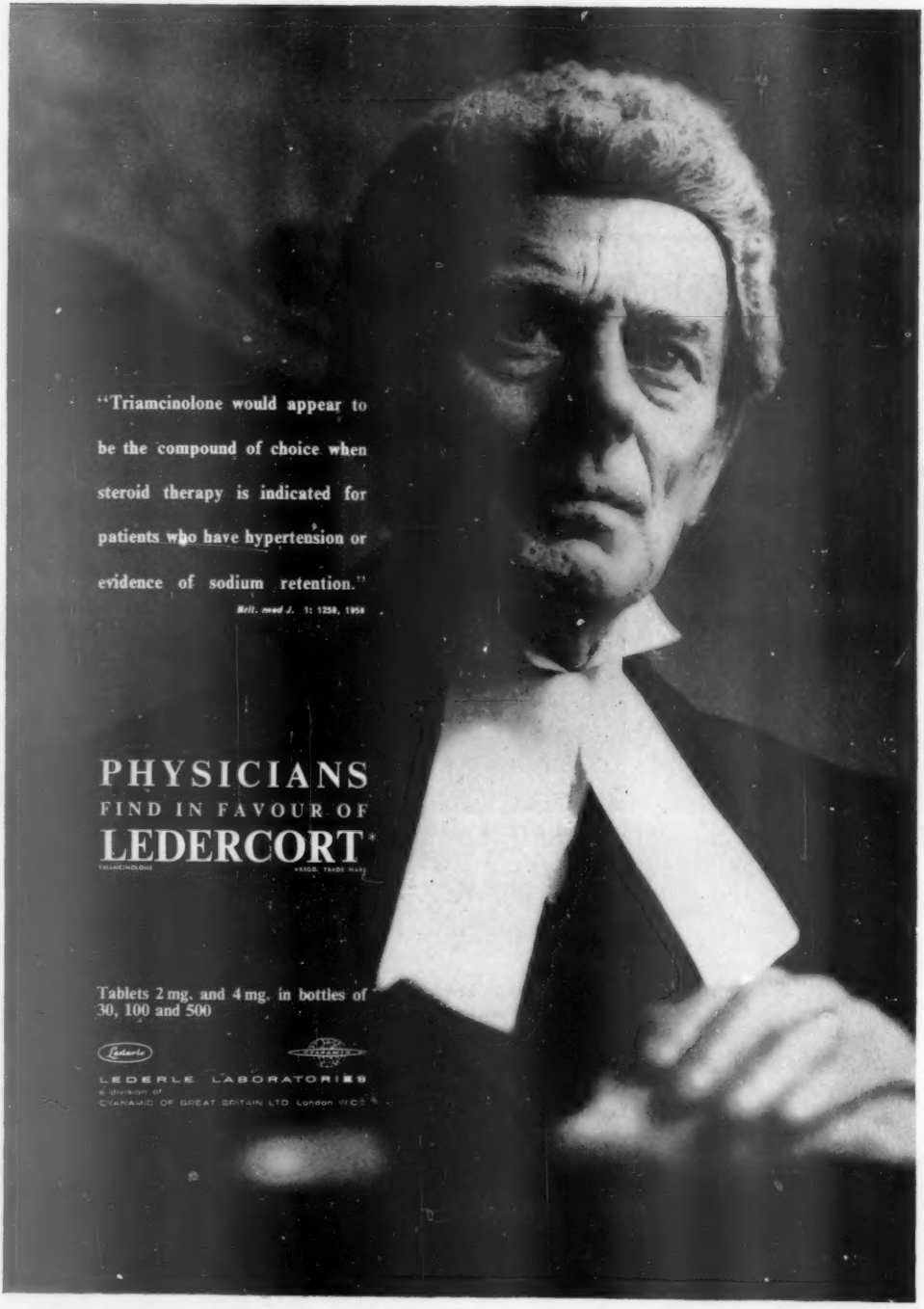
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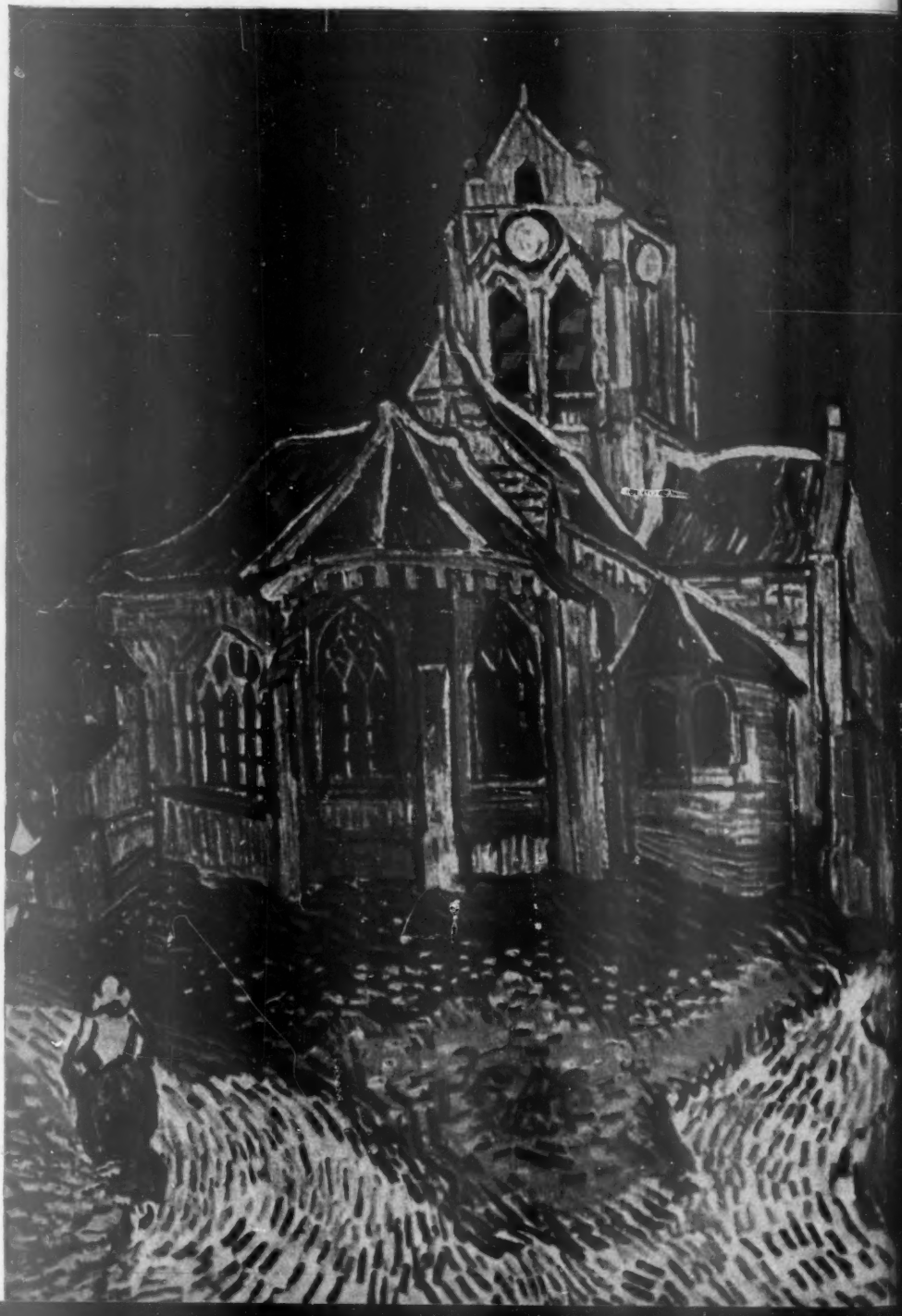

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